CLINICAL STUDY PROTOCOL

Title: A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone

Abbreviated Title: Evaluation of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy (AMETHYST-DN)

Investigational Product: RLY5016

EudraCT Number: 2011-000165-12

Protocol Number: RLY5016-205

Sponsor: Relypsa, Inc.
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Original Protocol Date: 22 February 2011
Amendment Number 1: 28 June 2011
Amendment Number 2: 23 March 2012
PROTOCOL REVIEW AND SIGNATURE FORM

Protocol Title: A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone

Protocol Number: RLY5016-205
Original Protocol Date: 22 February 2011
Amendment Number 1: 28 June 2011
Amendment Number 2: 23 March 2012

INVESTIGATOR STATEMENT

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and any applicable local and/or national laws and regulations as well as Institutional Review Board/Independent Ethics Committee requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal Investigator Signature ________________________________ Date

Principal Investigator Name (print)

SPONSOR STATEMENT

On behalf of Relypsa, Inc., I confirm that Relypsa, Inc. will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

Lance Berman, MD
Senior Vice President, Medical Affairs
Relypsa, Inc.

Date

23-March-2012

CONFIDENTIAL
# AMETHYST-DN – RLY5016-205
## PROTOCOL AMENDMENT #2
### SUMMARY AND RATIONALE FOR CHANGES

The following is a summary of the major changes made in this protocol amendment, the sections affected, and the rationale for each change.

<table>
<thead>
<tr>
<th>No.</th>
<th>Section(s)</th>
<th>Description of Changes</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>All</td>
<td><strong>Global Changes:</strong></td>
<td>Typographical / Administrative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Updated title page, Protocol and Review Signature Form, footers and text to reflect amended protocol version and date</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Updated the Table of Contents, Glossary, and References list</td>
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<tr>
<td></td>
<td></td>
<td>- Adjusted section and citations</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>- Corrected punctuation and formatting</td>
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</tr>
<tr>
<td>2.</td>
<td>Front Pages</td>
<td><strong>Title Page and Signature Form:</strong></td>
<td>Change of Sponsor personnel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical Monitor contact name and information updated for Dr. Lance Berman, Senior Vice President of Medical Affairs</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Synopsis</td>
<td><strong>Added Investigational Sites:</strong></td>
<td>To attain desired number of patients treated with RLY5016 for 12 months</td>
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<td></td>
<td></td>
<td>Increased (from initial 50 – 60 sites) to 80 – 90 sites</td>
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<td>4.</td>
<td>Synopsis, 3.4, 3.5.1</td>
<td><strong>Removed Enrollment Limits:</strong></td>
<td>Given the need to complete enrollment in this study, the enrollment limits for each stratum, cohort and dose group will be removed. The overall number of patients enrolled in the study (300) to provide long-term safety data will not change.</td>
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<td>- Removed the maximum number of patients to be enrolled in each stratum (150 per stratum), cohort (up to 100 in Cohort 3) and dose group (50 per group)</td>
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<td></td>
<td></td>
<td>- Deleted explanation of the purpose of the sequential run-in treatment strategy as this is no longer applicable</td>
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<td>5.</td>
<td>Synopsis, 3.3, 4.1, 7.3.10, 12.0</td>
<td><strong>Revised Eligibility Criteria (IC #3):</strong></td>
<td>Maintain consistency of screening eGFR values</td>
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<td>- Local eGFR value will be calculated using the CKD-EPI or MDRD equations</td>
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<td>- Reference to online eGFR calculator provided</td>
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<tr>
<td>6.</td>
<td>Synopsis, 3.3, 3.4, 4.1, 4.2</td>
<td><strong>Revised Eligibility Criteria (IC #7; Added EC #4):</strong></td>
<td>Eligibility criteria for uncontrolled hypertension in patients with CKD have been adjusted according to the JNC1 guidelines. In addition, the limits for study inclusion/exclusion have been clarified. Since patients in Cohort 3 with pre-existing hyperkalemia bypass the</td>
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<tr>
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<td>- Reduced SBP lower limit from ( \geq 140 ) to ( &gt; 130 ) mmHg</td>
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<td></td>
<td></td>
<td>- Changed SBP upper limit from ( &lt; 180 ) to ( \leq 180 ) mmHg</td>
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<tr>
<td></td>
<td></td>
<td>- Reduced DBP lower limit from ( \geq 90 ) to ( &gt; 80 ) mmHg</td>
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<td></td>
<td></td>
<td>- Changed DBP upper limit from ( &lt; 110 ) to ( \leq 110 ) mmHg</td>
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<td></td>
<td></td>
<td>- Made SBP and DBP limits inclusive to meet criterion (&quot;or&quot; changed to &quot;and&quot;)</td>
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<td>- Added for clarification: Patients without a history of hypertension can be enrolled</td>
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<td>- Defined exclusionary BP limit prior to beginning RLY5016 treatment (EC #4)</td>
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</table>
7. Synopsis, 4.2, Appendix A

**Added Exclusion Criteria (EC #5-7):**
- *Defined new serum magnesium value as exclusionary:* < 1.4 mg/dL (< 0.58 mmol/L) at screening based on central lab measurement, except for Cohort 3 patients whose serum magnesium will be evaluated based on local lab value
- *Defined new proteinuria limits as exclusionary:* Central lab urine ACR ≥ 10000 mg/g at screening (not applicable for hyperkalemic Cohort 3 patients)
- *Defined new pre-existing renal artery stenosis as exclusionary:* confirmed diagnosis or history of renal artery stenosis (unilateral or bilateral) as exclusionary

Run-In Period and do not receive maximal doses of a RAAS inhibitor, these subjects do not need to be hypertensive to qualify for study entry.

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1. Please see reference number 12 (Chobanian et al.) in Section 12.0 References

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8. Synopsis, 4.2

**Clarified Exclusion Criteria (Renumerated EC #10):**
Example of large bowel resection provided

Clarification

9. Synopsis, 4.2

**Clarified Exclusion Criteria (Renumerated EC #17):**
Entry criterion for liver enzyme values apply at Screening (S1) only

Clarification

10. Synopsis, 3.2, 3.6

**Clarified Wording for Timing of Long-Term Maintenance Visits:**
11 visits (M1-M11) in Long-Term Maintenance study period clarified as “monthly”

Clarification

11. Synopsis, 3.4

**Added Run-in Period Other Antihypertensive Treatment Usage:**
- Following the initiation of losartan and/or spironolactone, Cohort 1 and 2 patients may now add or modify non-RAAS inhibitor antihypertensive medication and antihypertensive drugs that do not affect serum potassium levels (e.g. calcium channel blockers, alpha-blockers, or alpha-2 agonists) per Investigator’s discretion
- *Added screen and enrollment failures reminder:* after beginning losartan and/or spironolactone, patients will discontinue study medications and return for unscheduled visit follow-up.

Provide additional options for Investigators to control blood pressure.

Makes synopsis consistent with protocol
|   | Synopsis, 3.5.2, 3.6.2, 5.5.1, 5.6.1 | **Clarified Exact Timing of RLY5016 Dosing When Dose is Adjusted (Treatment Initiation and Long-Term Maintenance Periods):**
If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day | Clarification |
|---|---|---|---|
| 12. | Synopsis, 3.5.3.3, 3.6.3.3, 3.6.3.4, 5.5.3 | **Revised Blood Pressure Control Guidelines During the Treatment Initiation and Long-Term Maintenance Periods:**
- Clarified the following: during the Treatment Initiation Period Cohort 2 and Cohort 3 patients must keep the dose(s) of pre-study ACEI and/or ARB unchanged.
- During the Long-Term Maintenance Period: patients in Cohorts 2 and 3 can be started on a new ACEI and/or ARB (up to maximum approved dose) for keeping blood pressure within target levels.
- Increased SBP limit that defines hypotension from < 90 to < 110 mmHg
- All patients who develop symptomatic hypotension or SBP < 110 mmHg (with or without symptoms) should either have non-RAAS inhibitor antihypertensive treatments removed or their doses reduced. For those patients on spironolactone, the spironolactone dose should be modified before the non-RAAS antihypertensive agents are modified if blood pressure continues to remain uncontrolled.
- Investigator’s discretion will determine any increases after halving of the spironolactone dose back to a maximum dose of 50 mg/day (if needed) for blood pressure control. | Provide additional options for Investigators to control blood pressure. |
| 13. | Synopsis, 3.5.3.4 | **Revised Other Antihypertensive Treatment Usage During the Treatment Initiation Period:**
- All patients may now add or modify non-RAAS inhibitor antihypertensives and antihypertensive drugs that do not affect serum potassium levels (e.g. calcium channel blockers, alpha-blockers, or alpha-2 agonists) per Investigator’s discretion
- For patients in Cohort 2 and Cohort 3, the dose(s) of pre-study ACEI and/or ARB medication must remain unchanged | Provide additional options for Investigators to control blood pressure |
| 14. | Synopsis, 3.5.3.4 | **Clarified Serum Potassium and Blood Pressure Monitoring and Control Procedures (Long-Term Maintenance Titration Algorithm):**
- Increased SBP limit from < 90 to < 110 mmHg (after lowering of spironolactone dose)
- *Added the following language:* “In order to check for any changes to serum potassium levels, patients who experience symptomatic hypotension or SBP < 110 mmHg and whose dose of spironolactone or ACEI/ARB is reduced, or any patients who require modification of RAAS inhibitor background treatment, should return for an unscheduled visit in 1 week. RLY5016 dose adjustment (if necessary) will be performed in accordance with this algorithm. If their serum potassium remains within the target range, they will resume the monthly | Ensures serum potassium monitoring while providing blood pressure control during the Long-Term Maintenance Period |
| 15. | Synopsis, 3.6.2 | --- | --- |
### 16. Synopsis, 3.6.2

**Inserted Rules for Withdrawal for Non-Responders (Long-Term Maintenance Titration Algorithm):**
Clarified the following: at any study visit, patients who are already on either the maximum RLY5016 dose of 60 g/d or the minimum dose of 0 g/d (no RLY5016 dispensed), AND who meet serum potassium criteria for RLY5016 dose increase or decrease, respectively, must be withdrawn from the study. The Investigator should provide standard of care and the patient should return for the follow-up visits (see Follow-up Period and Treatment Discontinuation section)

### 17. Synopsis, 3.6.3, 3.6.3.2, 3.6.3.3, 3.6.3.4

**Revised Concomitant Medication Usage During the Long-Term Maintenance Period:**
- Patients on pre-study ACEI and/or ARB (Cohorts 2 and 3) may add a new ACEI and/or ARB per Investigator discretion to maximum approved doses
- Increased SBP limit that defines halving of spironolactone dose from < 90 to < 110 mmHg
- If after modifying the dose of spironolactone, symptomatic hypotension or a SBP < 110 mmHg persists, non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced
- Investigator's discretion will determine any increases after halving of the spironolactone dose back to a maximum dose
- If the SBP > 160 mmHg or DBP > 100 mmHg, and changes are made to the patient's antihypertensive treatment, or if changes are made to the patient's antihypertensive treatment due to hypotension, the Investigator should bring the patient back for a blood pressure check within 1 to 2 weeks

### 18. Synopsis, 3.5.2, 3.6.2, 3.7, 6.7.2, App A, 9.7, 12.0

**Added Survival Follow-up Contact for Patients that Early Terminate (Telephone Calls):**
- Telephone contact(s) (every 3 months starting from the last Follow-up visit until one year after the patient’s Baseline T0 visit) to gather survival data will occur for up to one year for patients who discontinue from the study
- **Addition to Safety Analysis:** Due to the lack of a placebo control arm in this study, mortality rates reported in the study will be compared using cohort matching with historical mortality rates reported in the USRDS annual reports.

### 19. 4.3

**Revised Withdrawal Criteria:**
- Added “treated as per standard of care by the Investigator” for patients who withdraw
- Changed eGFR decrease from ≤ to < 10 mL/min/1.73m²
- Defined any SBP < 110 mmHg (with or without symptoms)
<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased SBP limit</td>
<td>From &lt; 90 to &lt; 110 mmHg and defines more exact dose adjustments expected: “dose of spironolactone reduced and/or other non-RAAS inhibitor agents have either been removed or doses have been decreased”</td>
</tr>
<tr>
<td>Added new hypertension criterion</td>
<td>Confirmed hypertension with either SBP &gt; 180 mmHg or DBP &gt; 110 mmHg (repeated 30 minutes after the initial readings) at any time during the study if the patient is on at least 3 antihypertensive agents.</td>
</tr>
<tr>
<td>Added new magnesium withdrawal limit</td>
<td>Serum magnesium &lt; 1.0 mg/dL (&lt; 0.42 mmol/L)</td>
</tr>
<tr>
<td>Added new proteinuria withdrawal limit</td>
<td>Urine ACR &gt; 10000 mg/g</td>
</tr>
</tbody>
</table>

### Deleted Reference to “Study Manual”:
- Communication of detailed instructions provided by other written means

### Clarified Exact Timing of Spironolactone and Losartan Initiation:
- Losartan treatment will be initiated the next morning following the R0 Visit in patients who receive losartan 100 mg/d (Cohort 1)
- The spironolactone 25 mg/d treatment may be initiated during the Run-In Period, in which case the first spironolactone dose should be taken the next morning and may be subsequently increased up to 50 mg/d before the T0 Visit or during the Long-Term Maintenance Period. If the spironolactone dose is adjusted, patients will start the new dose the next morning following the dose adjustment visit. Spironolactone may be taken for up to 60 weeks (including follow-up period) until its discontinuation.
- Revised wording of phrase: “During the Long-Term Maintenance Period, patients may start or maximize spironolactone dose up to 50 mg/d (if needed) for blood pressure control.”
- Allows spironolactone dose reduction and removal or reduction of non-RAAS inhibitor antihypertensive treatments at any time during either Treatment Initiation and/or Long-Term Maintenance: “If a patient develops symptomatic hypotension or SBP < 110 mmHg at any time during the study while on spironolactone, the spironolactone dose should be reduced in half: from 50 to 25 mg/d or from 25 mg/d to 25 mg every other day. Non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced. Dose of losartan or pre-study ACEI and or/ARB (whichever applies) should remain unchanged. Once blood pressure returns to normal the spironolactone dose may be increased to a maximum dose of 50 mg/d, at the Investigator’s discretion.”
<table>
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<tr>
<th></th>
<th></th>
<th><strong>Revised Prohibited Concomitant Medication Text:</strong> During the Treatment Initiation Period use of new ACEI and/or ARB drugs will be prohibited for patients who are assigned to Cohort 2 at the R0 Visit or Cohort 3 at the T0 Visit.</th>
<th>Clarification</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.</td>
<td>5.8.2</td>
<td><strong>Revised Allowed Concomitant Medication Text:</strong> Removed instructions to maintain constant dose of all antihypertensive medications including diuretics that do not affect serum potassium endpoints.</td>
<td>Consistency with greater Sponsor guidance on concomitant medications</td>
</tr>
<tr>
<td>24.</td>
<td>6.2.3</td>
<td><strong>Added New Criteria for Rescreening of Patients:</strong> Added GFR and ACR entry criteria to allowed reasons for rescreening per Investigator’s discretion</td>
<td>Reduces the inadvertent exclusion of patients due to variability in laboratory results</td>
</tr>
<tr>
<td>25.</td>
<td>6.4.1</td>
<td><strong>Corrected Typographical Error:</strong> M1 visit added to list of visits requiring urine ACR at 3 different time points</td>
<td>Clarification</td>
</tr>
<tr>
<td>26.</td>
<td>7.3.2, App A</td>
<td><strong>Added Serum Magnesium to New Confirmatory Local Lab Test at Screening (Cohort 3 only):</strong> Cohort 3 patients who require same day local lab analysis at Screening to meet eligibility (for ALT, AST and serum creatinine) will also include testing for serum magnesium</td>
<td>Consistency with revised entry criteria</td>
</tr>
</tbody>
</table>
| 27. | App A | **Revised Appendix A - Schedule of Events:** - Added telephone contacts during follow-up for patients that early terminate - Clarified Window Days on R0 and T0 Visits (footers updated accordingly)  
  - The maximum allowed window for R0 Visit is 10 days (calculated from the date of S1 Visit)  
  - The maximum allowed window for T0 Visit is 10 days (calculated from the date of previous study visit: S1, R0, R1, R2, or R3) | Consistency with addition of early term telephone contacts and clarification of Sponsor intention for Run-In Period study conduct |
| 28. | App F | **Revised Appendix F – End of Treatment / Early Termination Flowchart:** Added telephone contacts during follow-up for patients who discontinue from the study | Consistency with addition of follow-up telephone contacts |

*App = Appendix  
EC = Exclusion Criterion  
EDC = Electronic Data Capture  
IC = Inclusion Criterion*
## STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>TITLE</th>
<th>A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Number</td>
<td>RLY5016-205</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Description of Agent or Intervention:</td>
<td>RLY5016 is a non-absorbed, polymeric drug designed for the binding and removal of potassium from the gastrointestinal tract. RLY5016 is being developed for the treatment of hyperkalemia.</td>
</tr>
<tr>
<td>Study Design Overview</td>
<td>The study has two RLY5016 treatment periods: a Treatment Initiation Period for 8 weeks, followed by a Long-Term Maintenance Period for an additional 44 weeks which allows treatment with RLY5016 for up to a total of one year (i.e., 52 weeks). Eligible non-hyperkalemic patients will start a Run-In Period of 1 to 4 weeks in duration (Cohorts 1 and 2). Eligible hyperkalemic patients will start treatment with RLY5016 immediately (Cohort 3). At the first occurrence of serum potassium (K⁺) &gt; 5.0 – &lt; 6.0 mEq/L, eligible patients from all three cohorts will be assigned to one of two strata according to baseline serum potassium and will receive RLY5016 treatment at randomly assigned doses ranging from 10 to 40 g/day.</td>
</tr>
<tr>
<td>Study Duration</td>
<td>Up to 62 weeks per patient (including screening and follow-up procedures)</td>
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<tr>
<td>Study Sites</td>
<td>Approximately 80 to 90 sites globally</td>
</tr>
<tr>
<td>Study Population</td>
<td>Approximately 300 patients</td>
</tr>
</tbody>
</table>

## STUDY OBJECTIVES

### Primary
- To determine the optimal starting dose of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone

### Secondary
- To determine the efficacy of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone
- To determine the safety of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone
- To evaluate the chronic use of RLY5016
<table>
<thead>
<tr>
<th><strong>STUDY VARIABLES:</strong> Treatment Initiation Period (First 8 Weeks [or T0-T9 Visits])</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary Efficacy</strong></td>
</tr>
<tr>
<td>• Mean change in serum potassium from baseline (T0) to week 4 or prior to the initiation of RLY5016 dose titration (if occurs before week 4)</td>
</tr>
<tr>
<td><strong>Secondary Efficacy</strong></td>
</tr>
<tr>
<td>• Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration</td>
</tr>
<tr>
<td>• Proportion of patients maintaining the starting RLY5016 dose at weeks 4 and 8</td>
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<tr>
<td>• Mean change in serum potassium from baseline (T0) to post-baseline visits</td>
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<tr>
<td>• Mean change in serum potassium from end of RLY5016 treatment to follow-up visits</td>
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<tr>
<td>• Proportion of patients requiring RLY5016 titration</td>
</tr>
<tr>
<td>• Proportion of patients achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by end of week 8</td>
</tr>
<tr>
<td>• Mean time to first serum K⁺ in the range of 4.0 – 5.0 mEq/L</td>
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<tr>
<td>• Mean time to first RLY5016 titration</td>
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<tr>
<td>• Mean number of RLY5016 titrations</td>
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<tr>
<td>• Proportion of patients who maintain serum potassium in the range of 3.5 – 5.5 mEq/L by visit and during the entire Treatment Initiation Period</td>
</tr>
<tr>
<td>• Proportion of patients who maintain serum K⁺ in the range of 4.0 – 5.0 mEq/L by visit and during the entire Treatment Initiation Period</td>
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<tr>
<td>• Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria</td>
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<tr>
<td>• Mean change in blood pressure from Run-In Visit (R0) to weeks 4 and 8</td>
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<tr>
<td>• Mean change in urine albumin to creatinine ratio (ACR) from R0 to weeks 4 and 8</td>
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<tr>
<td>• Proportion of patients with ≥ 35% reduction in urine ACR from R0 to weeks 4 and 8</td>
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<tr>
<td>• Proportion of patients with urine ACR ≥ 500 mg/g at R0 who achieve ACR &lt; 500 mg/g at weeks 4 and 8</td>
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<tr>
<td>• Proportion of patients with urine ACR ≥ 300 mg/g at R0 who achieve ACR &lt; 300 mg/g at weeks 4 and 8</td>
</tr>
<tr>
<td><strong>Exploratory Measurements</strong></td>
</tr>
<tr>
<td>• Change in blood and urine biomarkers from R0 to T0, week 4 and week 8</td>
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<tr>
<td><strong>Safety</strong></td>
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<tr>
<td>Safety assessments will include the incidence and severity of adverse events, clinical laboratory variables, serum fluoride, vital signs (systolic and diastolic blood pressure, and heart rate) and ECG variables.</td>
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<tr>
<td>Other safety outcome measures are:</td>
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<tr>
<td>• Proportion of patients who meet &lt; 3.5 mEq/L serum K⁺ withdrawal criteria</td>
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<tr>
<td>• Incidence of hypomagnesemia (serum magnesium &lt; 1.8 mg/dL)</td>
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<tr>
<td>STUDY VARIABLES: Long-Term Maintenance Period (End of Week 8 [T9 Visit] to End of Week 52)</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td><strong>Primary Safety</strong></td>
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<td><strong>Secondary Safety</strong></td>
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<td><strong>Efficacy</strong></td>
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<td><strong>Exploratory Measurements</strong></td>
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**STUDY DESIGN**

**Description**

This is an open-label, randomized, dose ranging study to determine the optimal starting dose, efficacy and safety of RLY5016 in treating hyperkalemia in approximately 300 hypertensive patients with nephropathy due to type 2 diabetes mellitus (T2DM) receiving ACEI and/or ARB drugs, with or without spironolactone.
### STUDY DESIGN (cont’d)

<table>
<thead>
<tr>
<th>Description (cont’d)</th>
<th>The study consists of the following periods:</th>
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<tbody>
<tr>
<td></td>
<td>- Screening: up to 10 days (1 visit)</td>
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<tr>
<td></td>
<td>- Run-In: up to 4 weeks (1 to 4 visits)</td>
</tr>
<tr>
<td></td>
<td>- RLY5016 Treatment Initiation: first 8 weeks of RLY5016 treatment (a minimum of 10 visits)</td>
</tr>
<tr>
<td></td>
<td>- Long-Term Maintenance: additional 44 weeks of RLY5016 treatment up to a total of one year (minimum of 11 additional monthly visits)</td>
</tr>
<tr>
<td></td>
<td>- Follow-up (after RLY5016 discontinuation): 1 week (2 visits) OR 4 weeks (5 visits) depending on the final serum potassium level. Patients who discontinue from the study will be followed up for survival status (phone calls) from the date of their last visit up until one year after their Treatment Initiation date (Baseline, T0 Visit)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening</th>
<th>The screening period (up to 10 days) begins at the Screening Visit (S1). Upon completion of screening evaluations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ &lt; 4.3 mEq/L at the S1 Visit will be considered screen failures.</td>
</tr>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ 4.3 – 5.0 mEq/L, central lab estimated glomerular filtration rate (eGFR) 15 – &lt; 60 mL/min/1.73m², ACR ≥ 30 mg/g, systolic blood pressure (SBP) &gt; 130 – ≤ 180 mmHg and diastolic blood pressure (DBP) &gt; 80 – ≤ 110 mmHg, who meet all other eligibility criteria for patients without hyperkalemia, will return for the Run-In 0 (R0) Visit.</td>
</tr>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ &gt; 5.0 – &lt; 6.0 mEq/L (confirmed by same day re-test from a new blood draw), central lab eGFR 15 – &lt; 60 mL/min/1.73m² (calculated using CKD-EPI or MDRD equation) and who meet all other eligibility criteria for patients with hyperkalemia, will have the Visit S1 converted to Baseline Visit T0 and start RLY5016 treatment at the assigned dose (Cohort 3).</td>
</tr>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ ≥ 6.0 mEq/L (confirmed by same day re-test from a new blood draw) will be considered screen failures and should be managed at the discretion of the Investigator.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Run-In</th>
<th>The Run-In Period is intended to provide antihypertensive treatment with ACEI and/or ARB drugs, with or without spironolactone (up to 50 mg/d) until the patient achieves blood pressure control or develops hyperkalemia. At the Initial Run-In Visit (R0):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ &lt; 4.5 mEq/L at the R0 visit will be considered screen failures.</td>
</tr>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ 4.5 – 5.0 mEq/L, central lab eGFR 15 – &lt; 60 mL/min/1.73m², average R0 ACR ≥ 30 mg/g, SBP &gt; 130 – ≤ 180 mmHg and DBP &gt; 80 – ≤ 110 mmHg and who meet all other eligibility criteria for patients without hyperkalemia, will begin the Run-In Period Treatment according to the cohort assignment (Cohort 1 or 2).</td>
</tr>
<tr>
<td></td>
<td>- Patients with local lab serum K⁺ &gt; 5.0 – &lt; 6.0 mEq/L (confirmed by same day re-test from a new blood draw), central lab eGFR 15 – &lt; 60 mL/min/1.73m², and who meet all other eligibility criteria for patients with hyperkalemia, will have the R0 Visit converted to Baseline T0 Visit and start RLY5016 treatment at the assigned dose (Cohort 3).</td>
</tr>
<tr>
<td>STUDY DESIGN (cont’d)</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td>Run-In (cont’d)</td>
<td></td>
</tr>
<tr>
<td>• Patients with local lab serum K⁺ ≥ 6.0 mEq/L (confirmed by same day re-test from a new blood draw) will be considered screen failures and should be managed at the discretion of the Investigator.</td>
<td></td>
</tr>
<tr>
<td>The duration of the Run-In Period may be up to 4 weeks. The Run-In Period may include 1 to 4 visits. At the initial Run-In Visit (R0) patients with serum K⁺ 4.5 – 5.0 mEq/L who are taking at least one ACEI or ARB drug will discontinue all ACEI and/or ARB drugs and start losartan 100 mg/d (Cohort 1); however, based on Cohorts 1 and/or 3 enrollment data, Cohort 2 may be re-activated (as per the original study protocol dated 22 February 2011). Cohort 2 patients will remain on current ACEI and/or ARB drugs and start spironolactone 25 mg/d.</td>
<td></td>
</tr>
<tr>
<td>Assignment to cohort will be performed using an Interactive Voice/Web Response System (iXRS).</td>
<td></td>
</tr>
<tr>
<td>During the Run-In Period, in order to control blood pressure, following the initiation of losartan and/or spironolactone, Cohorts 1 and 2 patients will be allowed to add or modify non-RAAS inhibitors and antihypertensive drugs that do not affect blood potassium levels (e.g., calcium channel blocker, alpha-blocker, or alpha-2 agonist) per Investigator’s discretion.</td>
<td></td>
</tr>
<tr>
<td>At the first occurrence of a local lab serum K⁺ &gt; 5.0 – &lt; 6.0 mEq/L after the R0 Visit (R1 to R3 Visits) in either Cohort 1 or 2, eligible patients will start the RLY5016 Treatment Initiation Period.</td>
<td></td>
</tr>
<tr>
<td>Patients who develop serum K⁺ ≥ 6.0 mEq/L at any point during the Run-In Period (after the R0 Visit) will have a repeat serum potassium test as soon as possible on the same day from a new blood draw. If the repeat serum K⁺ is ≥ 6.0 mEq/L the patients will be considered enrollment failures and they must be discontinued from the study and treated per standard of care. These patients cannot be re-screened.</td>
<td></td>
</tr>
</tbody>
</table>

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## STUDY DESIGN (cont’d)

### Run-In (cont’d)

Depending on the Cohort assignment at the R0 Visit the sequence of events during the Run-In Period will differ and patients will continue the Run-In Period as follows:

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Run-In Day</th>
<th>Local Lab Serum K⁺, mEq/L</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cohort 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Losartan 100 mg</td>
</tr>
<tr>
<td>R0</td>
<td>0</td>
<td>&lt; 4.5</td>
<td>Screen failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 – 5.0</td>
<td>Discontinue ACEI and/or ARB + start LS 100 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Continue ACEI and/or ARB. Randomize (T0). <strong>Cohort 3 only</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 6.0</td>
<td>Screen failure</td>
</tr>
<tr>
<td>R1</td>
<td>7</td>
<td>≤ 5.0</td>
<td>Continue LS 100 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes – ↑ SP to 50 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No – Continue R0 Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 6.0</td>
<td>Enrollment failure</td>
</tr>
<tr>
<td>R2</td>
<td>14</td>
<td>≤ 5.0</td>
<td>SBP &gt; 130 or DBP &gt; 80 mmHg?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes – start SP 25 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No – Continue R1 Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 6.0</td>
<td>Enrollment Failure</td>
</tr>
<tr>
<td>R3</td>
<td>21</td>
<td>≤ 5.0</td>
<td>SBP &gt; 130 or DBP &gt; 80 mmHg?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Yes – ↑ SP up to 50 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No – Continue R2 Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 6.0</td>
<td>Enrollment Failure</td>
</tr>
<tr>
<td>T0</td>
<td>28</td>
<td>≤ 5.0 or ≥ 6.0</td>
<td>Enrollment failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
</tr>
</tbody>
</table>

BP – Blood pressure; LS – Losartan; SP – Spironolactone; Tx – Treatment

The average ACR value for R0 Visit (R0 ACR) will be calculated using up to 3 available ACR values from: S1 Visit, one day before R0 Visit, and R0 Visit. Patients in Cohorts 1 and 2 with average R0 ACR < 30 mg/g will be considered screen failures and must be discontinued from the study at the R1 Visit. These patients cannot be re-screened.

Patients with serum K⁺ ≤ 5.0 mEq/L at the end of the Run-In Period (T0 Visit) will be considered enrollment failures and cannot be re-screened.

Patients who are screen failures or enrollment failures after the initiation of Losartan and/or Spironolactone treatment should discontinue study medications and return for one unscheduled visit within 3 to 7 days.

## STUDY DESIGN: Treatment Initiation Period (First 8 Weeks [or T0-T9 Visits])

The Treatment Initiation T0 Visit (Baseline, Day 1) takes place when the patient develops serum K⁺ > 5.0 – < 6.0 mEq/L during the Run-In Period (Cohorts 1 and 2) OR at either the S1 or the R0 Visit (Cohort 3).
<table>
<thead>
<tr>
<th>Study Design: Treatment Initiation Period (First 8 Weeks [or T0-T9 Visits]) (cont’d)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomization to Starting Dose of RLY5016 (cont’d)</strong></td>
</tr>
<tr>
<td>Eligible patients will be assigned to one of two RLY5016 treatment strata:</td>
</tr>
<tr>
<td>- <strong>Stratum 1:</strong> Patients with serum K⁺ &gt; 5.0 – 5.5 mEq/L will be randomized in a 1:1:1 ratio to receive one of the following RLY5016 starting doses within each study cohort:</td>
</tr>
<tr>
<td>- 10 g/day (g/d)</td>
</tr>
<tr>
<td>- 20 g/d</td>
</tr>
<tr>
<td>- 30 g/d</td>
</tr>
<tr>
<td>- <strong>Stratum 2:</strong> Patients with serum K⁺ &gt; 5.5 – &lt; 6.0 mEq/L will be randomized in a 1:1:1 ratio to receive one of the following RLY5016 starting doses within each study cohort:</td>
</tr>
<tr>
<td>- 20 g/d</td>
</tr>
<tr>
<td>- 30 g/d</td>
</tr>
<tr>
<td>- 40 g/d</td>
</tr>
<tr>
<td>After randomization to the starting RLY5016 dose all patients will initiate treatment with RLY5016 on the evening of the Day 1 visit.</td>
</tr>
<tr>
<td>Randomization to RLY5016 doses will be performed using an IXRS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RLY5016 Treatment Initiation Titration Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients start RLY5016 treatment at their assigned dose level on the evening of Day 1 (after T0 Visit). They should continue taking losartan 100 mg/d (with or without spironolactone 25-50 mg/d) OR pre-study ACEI and/or ARB with spironolactone 25-50 mg/d, (as per their Cohort 1 or 2 assignment), as well as any other protocol-allowed antihypertensive therapy. Patients in Cohort 3 will continue their pre-study ACEI and/or ARB.</td>
</tr>
<tr>
<td><strong>RLY5016 Treatment Initiation Titration Algorithm:</strong></td>
</tr>
<tr>
<td>The starting RLY5016 dose may be titrated at any scheduled study visit beginning on Day 3 and ending on Day 50. The RLY5016 titration algorithm is designed to maintain serum K⁺ in the target range of 4.0 – 5.0 mEq/L.</td>
</tr>
<tr>
<td>All RLY5016 titration and discontinuation decisions will be provided by IXRS based on local lab serum potassium measurements.</td>
</tr>
<tr>
<td>If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day.</td>
</tr>
<tr>
<td>If at ANY time during the Treatment Initiation Period, a patient’s serum K⁺ value reported by the local lab is ≥ 6.2 mEq/L, the serum potassium test must be repeated as soon as possible on the same day from a new blood draw. If repeat serum K⁺ is:</td>
</tr>
<tr>
<td>- ≥ 6.2 mEq/L – The patient must be withdrawn from the study* and the Investigator should provide standard of care for hyperkalemia.</td>
</tr>
<tr>
<td>- &lt; 6.2 mEq/L – The patient should be treated by adjusting the RLY5016 dose in accordance with this algorithm.</td>
</tr>
<tr>
<td><strong>Day 3 Visit (T1):</strong></td>
</tr>
<tr>
<td>RLY5016 dose will only be adjusted at this visit if the local lab serum K⁺ value is:</td>
</tr>
<tr>
<td>- 5.8 – &lt; 6.2 mEq/L – RLY5016 dose increase to 60 g/d (first dose should be taken as the evening dose on the same day of the visit). The patient must return for a visit 1 day later for serum potassium re-evaluation. At this return visit, did serum K⁺ decrease by ≥ 0.4 mEq/L from Day 3 visit?</td>
</tr>
<tr>
<td>- Yes – No change in 60 g/d dose. The patient should return for next scheduled study visit (Day 8, T2).</td>
</tr>
<tr>
<td>RLY5016 Treatment Initiation Titration Algorithm (cont'd)</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>STUDY DESIGN: Treatment Initiation Period (First 8 Weeks [or T0-T9 Visits]) (cont'd)</td>
</tr>
<tr>
<td>o <strong>No</strong> – The patient must be withdrawn from the study*. The Investigator should provide standard of care for hyperkalemia.</td>
</tr>
<tr>
<td>o <strong>&lt; 3.5 mEq/L</strong> – RLY5016 dose decrease to 10 g/d or to 0 g/d if the patient is currently on 10 g/d. The patient must return for a visit 1 day later and if serum K⁺ at this return visit is:</td>
</tr>
<tr>
<td>o <strong>&lt; 3.5 mEq/L</strong> – The patient must be withdrawn from the study* with RLY5016 discontinued. The Investigator should provide standard of care for hypokalemia.</td>
</tr>
<tr>
<td>o <strong>3.5 – &lt; 4.0 mEq/L</strong> – RLY5016 dose decrease to 0 g/d (except for patients already on the minimum dose of 0 g/d, <strong>who must be withdrawn from the study</strong>). The patient should return for next scheduled study visit (Day 8, T2).</td>
</tr>
<tr>
<td>o <strong>≥ 4.0 mEq/L</strong> – No change in RLY5016 dose. The patient should return for next scheduled study visit (Day 8, T2).</td>
</tr>
<tr>
<td>Day 8 (T2), Day 15 (T3), Day 22 (T4), Day 29 (T5), Day 36 (T6), Day 43 (T7), and Day 50 (T8) Visits:</td>
</tr>
<tr>
<td>If local laboratory serum K⁺ value is within the <strong>4.0 – 5.0 mEq/L</strong> range, no titration of RLY5016 is required and the patient will continue the same RLY5016 dose until the next scheduled study visit.</td>
</tr>
<tr>
<td>The RLY5016 dose will only be adjusted if the local laboratory serum K⁺ value is:</td>
</tr>
<tr>
<td>o <strong>&gt; 5.5 – &lt; 6.2 mEq/L</strong> – Did serum K⁺ decrease by ≥ 0.4 mEq/L from previous scheduled visit one week ago?</td>
</tr>
<tr>
<td>o <strong>Yes</strong> – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, <strong>who must be withdrawn from the study</strong>).</td>
</tr>
<tr>
<td>o <strong>No</strong> – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, <strong>who must be withdrawn from the study</strong>). The patient must return for a visit 1, 2, or 3 days later (timing at the Investigator’s discretion). At this return visit (1, 2, or 3 days later), did serum K⁺ decrease by ≥ 0.4 mEq/L from previous visit?</td>
</tr>
<tr>
<td>o <strong>Yes</strong> – No change in RLY5016 dose. The patient will return for the next scheduled study visit.</td>
</tr>
<tr>
<td>o <strong>No</strong> – The patient must be withdrawn from the study*.</td>
</tr>
<tr>
<td>o <strong>&gt; 5.0 – 5.5 mEq/L</strong> – Did serum K⁺ decrease by ≥ 0.4 mEq/L from previous scheduled visit one week ago?</td>
</tr>
<tr>
<td>o <strong>Yes</strong> – No change in RLY5016 dose.</td>
</tr>
<tr>
<td>o <strong>No</strong> – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, <strong>who must be withdrawn from the study</strong>).</td>
</tr>
<tr>
<td>o <strong>3.5 – &lt; 4.0 mEq/L</strong> – RLY5016 dose decrease by 10 g/d (except for patients already on the minimum dose of 0 g/d, <strong>who must be withdrawn from the study</strong>).</td>
</tr>
<tr>
<td>o <strong>&lt; 3.5 mEq/L</strong> – RLY5016 dose decrease to 10 g/d or to 0 g/d (if the patient is currently on 10 g/d). The patients who are already on the minimum dose of 0 g/d must be withdrawn from the study**).</td>
</tr>
</tbody>
</table>
**STUDY DESIGN: Treatment Initiation Period (First 8 Weeks [or T0-T9 Visits]) (cont’d)**

<table>
<thead>
<tr>
<th>RLY5016 Treatment Initiation Titratio n Algorithm (cont’d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If serum $K^+$ remains $&lt; 3.5$ mEq/L for 2 consecutive scheduled visits (one week apart) regardless of RLY5016 dose, patient must be withdrawn from the study (with RLY5016 discontinued and the patient’s serum potassium treated per Investigator’s judgment) and return for the follow-up visits (see Follow-up Period and Treatment Discontinuation section).</td>
</tr>
</tbody>
</table>

* Patients discontinued per algorithm should attend follow-up visits (see Follow-up Period and Treatment Discontinuation section).

** At any of the following Study Visits: T2, T3, T4, T5, T6, T7, T8, and T9 patients who are already on either the maximum RLY5016 dose of 60 g/d or the minimum dose of 0 g/d (no RLY5016 dispensed), AND who meet serum potassium criteria for RLY5016 dose increase or decrease, respectively, must be withdrawn from the study. The Investigator should provide standard of care and the patient should return for the follow-up visits (see Follow-up Period and Treatment Discontinuation section).

**STUDY DESIGN: Long-Term Maintenance Period (End of Week 8 [T9 Visit] to End of Week 52)**

<table>
<thead>
<tr>
<th>Description of Long-Term Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Long-Term Maintenance period starts on Day 57 (T9 or Week 8 Visit) of the Treatment Initiation Period and lasts for 44 weeks until the end of Week 52 or the M11 Visit. Patients will continue treatment with RLY5016 for up to a total of one year (including the 8 weeks in the Treatment Initiation Period) and will have at a minimum 11 additional monthly visits: M1 to M11.</td>
</tr>
</tbody>
</table>

At the T9 Visit (Day 57) of the Treatment Initiation Period, patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits (occurring after T9) until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule. Titrations at the T9 Visit and all subsequent Weekly and Monthly Maintenance visits will be based on the Long-Term Maintenance titration algorithm.

<table>
<thead>
<tr>
<th>Long-Term Maintenance Titratio n Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>During the Long-Term Maintenance Period, the RLY5016 dose may be titrated at any scheduled study visit beginning at the T9 Visit (Week 8) and ending on Week 51. RLY5016 titration and discontinuation instructions will be provided by IXRS upon entry of respective local lab serum potassium value based on the following Long-Term Maintenance Titration Algorithm.</td>
</tr>
</tbody>
</table>

If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day.

**Long-Term Maintenance Titration Algorithm:**

At the T9, M1-M10 visits, if the local laboratory serum $K^+$ value is within the $3.8 - 5.0$ mEq/L range, no titration of RLY5016 is required and the patient will continue on the same RLY5016 dose until the next scheduled study visit.

If at ANY time during the study, a patient’s serum $K^+$ value reported by the local lab is $\geq 6.5$ mEq/L, the serum potassium test must be repeated as soon as possible on the same day from a new blood draw and if repeat serum $K^+$ is $\geq 6.5$ mEq/L, the patient must be withdrawn from the study and the Investigator should provide standard of care for hyperkalemia. The patient should return for the follow-up visits (see Follow-up Period and Treatment Discontinuation section).
<table>
<thead>
<tr>
<th>Long-Term Maintenance Titration Algorithm (cont’d)</th>
<th>RLY5016 dose titration at the <strong>T9, M1-M10 visits</strong> will be based on the following serum K⁺ value ranges:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>≥ 6.5 mEq/L</strong> (confirmed by same day re-test) – The patient must be withdrawn from the study* and the Investigator should provide standard of care for hyperkalemia.</td>
<td></td>
</tr>
<tr>
<td>• <strong>6.0 – &lt; 6.5 mEq/L</strong> – RLY5016 dose increase by 10 g/d or more (per Investigator's discretion) up to the maximum of 60 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**). ECG must be performed. RAAS inhibitors should be continued at the same dose. The patient must return for mandatory safety visit scheduled 1, 2, or 3 days later (1st visit) AND may require another visit 7 days after the visit when RLY5016 dose was increased (2nd visit).</td>
<td></td>
</tr>
<tr>
<td>If at the 1st mandatory safety visit (1,2 or 3 days later) serum K⁺ is:</td>
<td></td>
</tr>
<tr>
<td>o <strong>≥ 6.5 mEq/L</strong> – the patient must be withdrawn from the study*</td>
<td></td>
</tr>
<tr>
<td>o <strong>6.0 – &lt; 6.5 mEq/L</strong> – either:</td>
<td></td>
</tr>
<tr>
<td>• No change in RLY5016 dose. Reduce RAAS inhibitor dose and re-check serum potassium at the 2nd visit (7 days after the RLY5016 dose was increased)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>• The patient must be withdrawn from the study* and the Investigator should provide standard of care for hyperkalemia</td>
<td></td>
</tr>
<tr>
<td>o <strong>&lt; 6.0 mEq/L</strong> – No change in RLY5016 dose; no change in RAAS inhibitor dose; patient must attend the 2nd mandatory safety visit.</td>
<td></td>
</tr>
<tr>
<td>At the 2nd mandatory safety visit, patients who continue participation in the study must return for Weekly Maintenance Visits and have RLY5016 dose adjustment performed in accordance with this algorithm. Once patients have been on the same dose of RLY5016 for 3 consecutive weekly visits, they may resume the monthly visit schedule.</td>
<td></td>
</tr>
<tr>
<td>• <strong>&gt; 5.5 – &lt; 6.0 mEq/L</strong> – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**). Patient should return in 1 week for RLY5016 dose adjustment as needed in accordance with this algorithm.</td>
<td></td>
</tr>
<tr>
<td>• <strong>&gt; 5.0 – 5.5 mEq/L</strong> – No change in RLY5016 dose. Patient should return in 1 week. If at that visit serum K⁺ is:</td>
<td></td>
</tr>
<tr>
<td>o <strong>&gt; 5.0 – 5.5 mEq/L</strong> – RLY5016 dose increase by 10 g/d**. Patient should return in 1 week for RLY5016 dose adjustment as needed in accordance with this algorithm.</td>
<td></td>
</tr>
<tr>
<td>o <strong>≤ 5.0 OR &gt; 5.5 mEq/L</strong> – RLY5016 dose adjustment is performed in accordance with this algorithm.</td>
<td></td>
</tr>
<tr>
<td>• <strong>3.5 – &lt; 3.8 mEq/L</strong> – No change in RLY5016 dose. Patient should return in 1 week. If at that visit serum K⁺ is:</td>
<td></td>
</tr>
<tr>
<td>o <strong>3.5 – &lt; 3.8 mEq/L</strong> – RLY5016 dose decrease by 10 g/d (except for patients already on the minimum dose of 0 g/d, who must be withdrawn from the study**). Patient should return in 1 week for RLY5016 dose adjustment as needed in accordance with this algorithm.</td>
<td></td>
</tr>
<tr>
<td>o <strong>&lt; 3.5 OR ≥ 3.8 mEq/L</strong> – RLY5016 dose adjustment is performed in accordance with this algorithm.</td>
<td></td>
</tr>
<tr>
<td>STUDY DESIGN: Long-Term Maintenance Period (End of Week 8 [T9 Visit] to Week 52) (cont’d)</td>
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<tr>
<td>---------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Long-Term Maintenance Titration Algorithm (cont’d)</strong></td>
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<tr>
<td>• &lt; 3.5 mEq/L – RLY5016 dose decrease to 0 g/d (except for patients already on the minimum dose of 0 g/d who must be withdrawn from the study**). ECG must be performed and the patient must return for two mandatory safety visits scheduled 1, 2, or 3 days (1st visit) AND 7 days (2nd visit) after the visit when RLY5016 dose was decreased. If serum K⁺ is:</td>
<td></td>
</tr>
<tr>
<td>o &lt; 3.5 mEq/L at either visit – The patient must be withdrawn from the study*. The Investigator should provide standard of care for hypokalemia.</td>
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</tr>
<tr>
<td>o ≥ 3.5 mEq/L at both visits – The patient should continue participation in the study and return for Weekly Maintenance Visits, when RLY5016 dose will be adjusted in accordance with this algorithm. Once patients have been on the same dose RLY5016 for 3 consecutive weekly visits, they may resume the monthly visit schedule.</td>
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<tr>
<td>o Patients who remain on 0 g/d of RLY5016 for 4 consecutive weekly visits will be discontinued from the study*.</td>
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</tr>
<tr>
<td>In order to check for any changes in serum potassium levels, patients who experience symptomatic hypotension or SBP &lt; 110 mmHg and whose dose of spironolactone or ACEI/ARB is reduced, or any patients who require modification of RAAS inhibitor background treatment, should return for an unscheduled visit in 1 week. RLY5016 dose adjustment (if necessary) will be performed in accordance with this algorithm. If their serum potassium remains within the target range, they will resume the monthly visit schedule.</td>
<td></td>
</tr>
<tr>
<td>* Patients discontinued per the algorithm should attend follow-up visits (see Follow-up Period and Treatment Discontinuation section).</td>
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</tr>
<tr>
<td>** At any study visit, patients who are already on either the maximum RLY5016 dose of 60 g/d or the minimum dose of 0 g/d (no RLY5016 dispensed), AND who meet serum potassium criteria for RLY5016 dose increase or decrease, respectively, must be withdrawn from the study. The Investigator should provide standard of care and the patient should return for the follow-up visits (see Follow-up Period and Treatment Discontinuation section).</td>
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</tr>
<tr>
<td><strong>Follow-up Period and Treatment Discontinuation</strong></td>
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<tr>
<td>At the End of RLY5016 Treatment or at the Early Termination Visit (any time after T0 to M11/ET Visit):</td>
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<tr>
<td>• Patients with final local lab serum K⁺ ≤ 5.0 mEq/L will discontinue RLY5016 but continue all RAAS inhibitors for 28 additional days, and will return for 5 follow-up visits F1, F2, F3, F4 and F5 scheduled in 3, 7, 14, 21, and 28 days, respectively, after RLY5016 discontinuation.</td>
<td></td>
</tr>
<tr>
<td>• Patients with final local lab serum K⁺ &gt; 5.0 mEq/L will discontinue RLY5016 and all RAAS inhibitors and will return for the follow-up visits F1 and F2 scheduled in 3 and 7 days, respectively, after RLY5016 discontinuation.</td>
<td></td>
</tr>
<tr>
<td>For those patients who discontinue from the study, additional survival data will be collected after the last performed study visit and will consist of telephone contacts conducted every 3 months starting from the last study visit until one year after the patient’s Baseline T0 Visit.</td>
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</tr>
</tbody>
</table>
**STUDY TREATMENTS**

| **Dose and Route of RLY5016 Administration** | RLY5016 will be taken orally twice daily in equally divided doses for up to 52 weeks starting on Day 1 (the evening dose only). Patients will take RLY5016 twice a day with their regular meals (breakfast and dinner).

RLY5016 dose will be adjusted as needed according to the appropriate titration algorithm (Treatment Initiation or Long-Term Maintenance) starting on Day 3 and up to the Week 51 Visit.

The minimum allowed dose is 0 g/d (no RLY5016 dispensed) and the maximum dose is 60 g/d. |
| --- | --- |

| **Per-protocol Study Medications** | **Losartan:**

Patients who receive losartan 100 mg/d (Cohort 1) at the R0 Visit will continue this regimen throughout the entire treatment period. Depending on the final local lab serum potassium level, some patients may continue on losartan until the end of the 4 week Follow-up Period.

**ACEI/ARB drugs:**

Patients who continue on pre-study ACEI and/or ARB drugs (Cohorts 2 and 3) should maintain stable doses throughout Run-In (if applicable) and the Treatment Initiation Period. After the start of the Long-Term Maintenance Period, doses of pre-study ACEI and/or ARB drugs may be increased if needed for blood pressure control up to the highest approved dose or new ACEI and/or ARB drugs may be initiated per Investigator’s discretion.

**Spironolactone:**

Patients on spironolactone will continue on the same (T0) dose throughout the Treatment Initiation Period. During the Long-Term Maintenance Period, patients may start or maximize spironolactone dose up to 50 mg/d (if needed) for blood pressure control.

If a patient develops symptomatic hypotension or SBP < 110 mmHg at any time during the study while on spironolactone, the spironolactone dose should be reduced in half (e.g., from 50 to 25 mg/d or from 25 mg/d to 25 mg every other day). If blood pressure continues to remain uncontrolled, non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced. Dose of losartan or pre-study ACEI and/or ARB (whichever applies) should remain unchanged. Once blood pressure returns to normal the spironolactone dose may be increased to a maximum dose of 50 mg/d, at the Investigator’s discretion. |
| --- | --- |

| **Other Antihypertensive Treatment** | **Run-In Period:**

During the Run-In Period, following the initiation of losartan and/or spironolactone, Cohort 1 and 2 patients will be allowed to add or modify non-RAAS inhibitors and antihypertensive drugs that do not affect blood potassium levels (e.g., calcium channel blocker, alpha-blocker, or alpha-2 agonist) per Investigator’s discretion.

**Treatment Initiation Period:**

During the Treatment Initiation Period all patients will be allowed to add or modify non-RAAS inhibitors and antihypertensive drugs that do not affect blood potassium levels (e.g., calcium channel blocker, alpha-blocker, or alpha-2 agonist) per Investigator’s discretion. |
If during the Treatment Initiation Period, a patient develops symptomatic hypotension or SBP < 110 mmHg (with or without symptoms), non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced. For those patients on spironolactone, the spironolactone dose should be modified before the non-RAAS antihypertensive agents are modified.

For patients in Cohort 2 and Cohort 3, the dose(s) of pre-study ACEI and/or ARB medication must remain unchanged.

Long-Term Maintenance Period:

After the start of the Long-Term Maintenance Period, if additional blood pressure reduction is required in order to achieve target levels (SBP < 130 or DBP < 80 mmHg) according to guidelines, the following sequence of drug changes should be considered:

1) For patients in Cohort 1 on Losartan 100 mg/d alone, an ACEI may be added and increased to the maximum approved dose
2) For patients in Cohort 2 and Cohort 3 either:
   a) the dose of pre-study ACEI and/or ARB should be increased to maximum approved doses, OR
   b) a new ACEI and/or ARB should be started and increased to maximum approved doses
3) Spironolactone should be started at 25 mg/d or increased up to 50 mg/d
4) Calcium channel blockers or beta blockers can be added
5) Diuretics should be used for the treatment of volume overload or if additional blood pressure control is necessary

During the Long-Term Maintenance Period, if the SBP is > 160 mmHg or DBP is > 100 mmHg, and changes are made to the patient’s antihypertensive treatment, or if changes are made to the patient’s antihypertensive treatment due to hypotension, the Investigator should bring the patient back for a blood pressure check within 1 to 2 weeks.

**ELIGIBILITY CRITERIA**

**Inclusion Criteria**

Patients must meet ALL of the following inclusion criteria:

1. Age 30 – 80 years old at screening
2. Type 2 diabetes mellitus (T2DM) diagnosed after age 30 which has been treated with oral medications or insulin for at least one year prior to screening
3. Chronic kidney disease: eGFR 15 – < 60 mL/min/1.73m² at screening based on central lab serum creatinine measurement (except for patients with hyperkalemia at S1, whose eligibility will be assessed based on local lab eGFR value calculated using CKD-EPI or MDRD equation)
4. Urine ACR:
   a) **Cohorts 1 and 2:** urine ACR ≥ 30 mg/g at screening (S1) AND average urine ACR ≥ 30 mg/g at the beginning of Run-In Period (R0) based on up to 3 ACR values obtained starting at S1 and ending at the R0 Visit
   b) **Cohort 3:** not applicable
### Inclusion Criteria (cont’d)

<table>
<thead>
<tr>
<th>5. Local laboratory serum K⁺ values of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) <strong>Cohorts 1 and 2:</strong> 4.3 – 5.0 mEq/L at S1; AND 4.5 – 5.0 mEq/L at R0; AND &gt; 5.0 – &lt; 6.0 mEq/L at randomization to RLY5016 (Baseline, T0 Visit)</td>
</tr>
<tr>
<td>b) <strong>Cohort 3:</strong> &gt; 5.0 – &lt; 6.0 mEq/L at S1 OR at R0 after same day confirmation</td>
</tr>
<tr>
<td>6. Must be receiving an ACEI and/or ARB for at least 28 days prior to screening</td>
</tr>
<tr>
<td>7. Any patient with a history of hypertension must have average SBP &gt; 130 – ≤ 180 mmHg AND average DBP &gt; 80 – ≤ 110 mmHg (sitting) at both screening and R0 (as applicable). While Cohorts 1 and 2 patients must have a diagnosis of hypertension to be enrolled in the study, Cohort 3 patients without a history of hypertension can be enrolled.</td>
</tr>
<tr>
<td>8. Females of child-bearing potential must be non-lactating, must have a negative serum pregnancy test at screening, and must have used a highly effective form of contraception for at least 3 months before RLY5016 administration, during the study, and for one month after study completion</td>
</tr>
<tr>
<td>9. Provide their written informed consent prior to participation in the study</td>
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</table>

### Exclusion Criteria

<table>
<thead>
<tr>
<th>Patients must NOT meet ANY of the following exclusion criteria:</th>
</tr>
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<tbody>
<tr>
<td>1. Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>2. Central lab hemoglobin A1c &gt; 12% at S1 (except for Cohort 3 patients who are hyperkalemic at S1)</td>
</tr>
<tr>
<td>3. Emergency treatment for T2DM within the last 3 months</td>
</tr>
<tr>
<td>4. A confirmed SBP &gt; 180 mmHg or DBP &gt; 110 mmHg at any time during Screening or Run-In Period or at Baseline T0 Visit</td>
</tr>
<tr>
<td>5. Central lab serum magnesium &lt; 1.4 mg/dL (&lt; 0.58 mmol/L) at screening (Cohort 3 patients will be evaluated based on local lab serum magnesium measurement)</td>
</tr>
<tr>
<td>6. Central lab urine ACR ≥ 10000 mg/g at screening (except for Cohort 3 patients who are hyperkalemic at S1)</td>
</tr>
<tr>
<td>7. Confirmed diagnosis or history of renal artery stenosis (unilateral or bilateral)</td>
</tr>
<tr>
<td>8. Diabetic gastroparesis</td>
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<td>9. Non-diabetic chronic kidney disease</td>
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<tr>
<td>10. History of bowel obstruction, swallowing disorders, severe gastrointestinal disorders or major gastrointestinal surgery (e.g., large bowel resection)</td>
</tr>
<tr>
<td>11. Current diagnosis of NYHA Class III or IV heart failure</td>
</tr>
<tr>
<td>12. Body mass index (BMI) ≥ 40 kg/m²</td>
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<tr>
<td>13. Any of the following events having occurred within 2 months prior to screening: unstable angina as judged by the Investigator, unresolved acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, transient ischemic attack or stroke, use of any intravenous cardiac medication</td>
</tr>
<tr>
<td>14. Prior kidney transplant, or anticipated need for transplant during study participation</td>
</tr>
<tr>
<td>15. Active cancer, currently on cancer treatment or history of cancer in the past two years except for non-melanocytic skin cancer which is considered cured</td>
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</table>
ELIGIBILITY CRITERIA (cont’d)

<table>
<thead>
<tr>
<th>Exclusion Criteria (cont’d)</th>
<th>16. History of alcoholism or drug/chemical abuse within 1 year</th>
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<tbody>
<tr>
<td></td>
<td>17. <strong>Central</strong> lab liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] &gt; 3 times upper limit of normal at S1 (except for Cohort 3 patients with hyperkalemia at S1, who will have <strong>local</strong> lab ALT and AST)</td>
</tr>
<tr>
<td></td>
<td>18. Loop and thiazide diuretics or other antihypertensive medications (calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent) that have not been stable for at least 28 days prior to screening or not anticipated to remain stable during study participation</td>
</tr>
<tr>
<td></td>
<td>19. Current use of polymer-based drugs (e.g., sevelamer, sodium polystyrene sulfonate, colesevelam, colestipol, cholestyramine), phosphate binders (e.g., lanthanum carbonate), or other potassium binders, or their anticipated need during study participation</td>
</tr>
<tr>
<td></td>
<td>20. Current use of lithium</td>
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<tr>
<td></td>
<td>21. Use of potassium sparing medications, including aldosterone antagonists (e.g., spironolactone), drospirenone, potassium supplements, bicarbonate or baking soda in the last 7 days prior to screening</td>
</tr>
<tr>
<td></td>
<td>22. Use of any investigational product within 30 days or 5 half-lives, whichever is longer, prior to screening</td>
</tr>
<tr>
<td></td>
<td>23. Inability to consume the investigational product, or, in the opinion of the Investigator, inability to comply with the protocol</td>
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<tr>
<td></td>
<td>24. In the opinion of the Investigator, any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the patient or affect the validity of the trial results</td>
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STATISTICAL METHODS

<p>| Determination of Sample Size | This study will have approximately 300 patients randomized (50 patients per dose group) to ensure at least 252 patients (42 patients per dose group) will receive investigational product and provide primary efficacy data for data analysis assuming a 15% non-evaluable rate. A sample size of 42 patients for each RLY5016 dose group is based on an effect size of 0.5 for the primary efficacy measurement, change in serum K⁺ from baseline to Week 4 or prior to the initiation of RLY5016 dose titration. This sample size will have 90% power to detect statistically significant change at significant level of 0.05 within each dose group. This calculation is based on a two-sided one sample paired t-test and a significance level of ( \alpha = 0.05 ). |
| Randomization | Eligible non-hyperkalemic patients will receive losartan 100 mg/d and spironolactone will be added as needed for blood pressure control (Cohort 1). Based on enrollment data in Cohorts 1 and/or 3, Cohort 2 (pre-study ACEI and/or ARB and spironolactone starting dose of 25 mg/d) may be re-activated. Eligible hyperkalemic patients will be assigned to Cohort 3 and will continue on their current ACEI and/or ARB. Each cohort will be stratified according to baseline serum potassium: Stratum 1 (serum K⁺ &gt; 5.0 – 5.5 mEq/L) and Stratum 2 (serum K⁺ &gt; 5.5 – &lt; 6.0 mEq/L). |</p>
<table>
<thead>
<tr>
<th>STATISTICAL METHODS (cont’d)</th>
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</thead>
<tbody>
<tr>
<td><strong>Randomization (cont’d)</strong></td>
<td>Patients in Stratum 1 will be randomized in a 1:1:1 allocation ratio to receive one of three RLY5016 starting doses: 10, 20, or 30 g/d within each study cohort. Patients in Stratum 2 will be randomized in a 1:1:1 allocation ratio to receive one of three RLY5016 starting doses: 20, 30, or 40 g/d within each study cohort.</td>
</tr>
<tr>
<td><strong>Analysis Population and Pooling of Investigators</strong></td>
<td>The main analysis of the primary efficacy parameter and secondary efficacy parameters will include intent-to-treat (ITT) population. The ITT population includes all randomized patients who received investigational product. Efficacy data collected from all study centers will be pooled for data analysis.</td>
</tr>
<tr>
<td><strong>Tests of Hypothesis and Significance Levels</strong></td>
<td>The primary null hypothesis to be tested in this study is that the least squares estimate of the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration within each RLY5016 dose group equals zero. The statistical tests used for the analysis of baseline variables and efficacy parameters will be performed at the $\alpha = 0.05$ significance level. All tests are two-sided.</td>
</tr>
<tr>
<td><strong>Methods for the Analysis of Primary Efficacy Measurement</strong></td>
<td>A parallel lines analysis of covariance (ANCOVA) model will be used for the analysis of the primary efficacy measurement. This ANCOVA model will include the treatment factor and baseline serum potassium as the covariate. The least squares estimate of the mean change of each treatment and its 95% confidence interval (CI) will be presented. A 95% CI of the pairwise difference between any two RLY5016 dose groups in the mean change of serum potassium will be constructed.</td>
</tr>
<tr>
<td><strong>Analysis of Safety Data</strong></td>
<td>Safety variables consist of adverse events, cardiovascular events, renal events, clinical laboratory test results, vital signs, clinically significant ECG findings, newly observed physical examination abnormalities, and termination data. All randomized patients who received at least one dose of RLY5016 will be included in the analysis and summaries of safety data.</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. INTRODUCTION AND RATIONALE</td>
<td>27</td>
</tr>
<tr>
<td>1.1. Background</td>
<td>27</td>
</tr>
<tr>
<td>1.2. Description of Investigational Product</td>
<td>30</td>
</tr>
<tr>
<td>1.3. Summary of Nonclinical and Clinical Experience</td>
<td>30</td>
</tr>
<tr>
<td>1.3.1. Nonclinical Pharmacology</td>
<td>31</td>
</tr>
<tr>
<td>1.3.2. Nonclinical Safety</td>
<td>31</td>
</tr>
<tr>
<td>1.3.3. Clinical Experience</td>
<td>33</td>
</tr>
<tr>
<td>1.3.3.1. Phase 1 Studies in Healthy Subjects (RLY5016-101 and RLY5016-102)</td>
<td>33</td>
</tr>
<tr>
<td>1.3.3.2. Phase 2a Study in Hemodialysis Patients (RLY5016-201)</td>
<td>34</td>
</tr>
<tr>
<td>1.3.3.3. Phase 2 Placebo-Controlled Study in Heart Failure Patients (RLY5016-202)</td>
<td>35</td>
</tr>
<tr>
<td>1.3.3.4. Phase 2 Dose Titration Study in Heart Failure and Chronic Kidney Disease Patients (RLY5016-204)</td>
<td>36</td>
</tr>
<tr>
<td>1.4. Rationale for Study Design</td>
<td>38</td>
</tr>
<tr>
<td>1.4.1. Rationale for Run-In</td>
<td>38</td>
</tr>
<tr>
<td>1.4.2. Rationale for RLY5016 Starting Doses</td>
<td>39</td>
</tr>
<tr>
<td>1.4.3. Rationale for the Long-Term Maintenance Period</td>
<td>40</td>
</tr>
<tr>
<td>1.4.4. Rationale for RLY5016 Dose Titration</td>
<td>40</td>
</tr>
<tr>
<td>1.4.5. Rationale for Continuation of RAAS Inhibitors after RLY5016 Discontinuation</td>
<td>41</td>
</tr>
<tr>
<td>1.5. Summary of Known and Potential Benefits and Risks</td>
<td>42</td>
</tr>
<tr>
<td>1.5.1. Potential Benefits of Treatment with RLY5016</td>
<td>42</td>
</tr>
<tr>
<td>1.5.2. Benefits of Optimal RAAS Blockade</td>
<td>43</td>
</tr>
<tr>
<td>1.5.3. Potential Risks of Treatment with RLY5016</td>
<td>44</td>
</tr>
<tr>
<td>1.5.4. Risks of Treatment with RAAS Inhibitors</td>
<td>45</td>
</tr>
<tr>
<td>1.5.5. Risks of Diabetic Nephropathy</td>
<td>46</td>
</tr>
<tr>
<td>2. OBJECTIVES</td>
<td>47</td>
</tr>
<tr>
<td>3. STUDY DESIGN</td>
<td>47</td>
</tr>
<tr>
<td>3.1. Description</td>
<td>47</td>
</tr>
<tr>
<td>3.2. Study Periods</td>
<td>49</td>
</tr>
<tr>
<td>3.3. Screening Period</td>
<td>50</td>
</tr>
<tr>
<td>3.4. Run-In Period</td>
<td>50</td>
</tr>
<tr>
<td>3.5. RLY5016 Treatment Initiation Period</td>
<td>53</td>
</tr>
<tr>
<td>3.5.1. Randomization to the Starting RLY5016 Dose</td>
<td>53</td>
</tr>
<tr>
<td>3.5.2. Treatment Initiation Period Titration Algorithm</td>
<td>54</td>
</tr>
<tr>
<td>3.5.2.1. Day 3 Visit (T1):</td>
<td>55</td>
</tr>
<tr>
<td>3.5.2.2. Day 8 (T2), Day 15 (T3), Day 22 (T4), Day 29 (T5), Day 36 (T6), Day 43 (T7), and Day 50 (T8) Visits:</td>
<td>55</td>
</tr>
</tbody>
</table>
3.5.3. Treatment Initiation Period – Per-Protocol Concomitant Medications. 57
  • 3.5.3.1. Losartan: ................................................................. 57
  • 3.5.3.2. ACEI/ARB drugs: ................................................ 57
  • 3.5.3.3. Spironolactone: .................................................. 58
  • 3.5.3.4. Other Antihypertensive Treatment: ................. 58

3.6. Long-Term Maintenance Period ................................................. 58
  3.6.1. RLY5016 Stabilization ......................................................... 59
  3.6.2. Long-Term Maintenance Period Titration Algorithm ........ 59
  3.6.3. Long-Term Maintenance Period – Per-Protocol Concomitant Medications .................................................. 62
    • 3.6.3.1. Losartan: ................................................................. 62
    • 3.6.3.2. ACEI/ARB drugs: ................................................ 62
    • 3.6.3.3. Spironolactone: .................................................. 63
    • 3.6.3.4. Other Antihypertensive Treatment: ................. 63

3.7. Follow-up Period ........................................................................ 64
3.8. Blinding ...................................................................................... 65
3.9. Choice of Study Design .............................................................. 65

4. SELECTION AND WITHDRAWAL OF PATIENTS ...................... 65
  4.1. Inclusion Criteria ...................................................................... 65
  4.2. Exclusion Criteria ..................................................................... 66
  4.3. Withdrawal Criteria ................................................................. 67

5. STUDY TREATMENTS .................................................................. 70
  5.1. Investigational Product: RLY5016 ............................................. 70
    5.1.1. Formulation, Packaging, and Labeling ............................... 70
    5.1.2. Storage ............................................................................ 70
    5.1.3. Preparation ....................................................................... 70
  5.2. Losartan .................................................................................. 70
    5.2.1. Formulation, Packaging, and Labeling ............................... 70
    5.2.2. Storage ............................................................................ 70
    5.2.3. Preparation ....................................................................... 71
  5.3. Spironolactone ........................................................................ 71
    5.3.1. Formulation, Packaging, and Labeling ............................... 71
    5.3.2. Storage ............................................................................ 71
    5.3.3. Preparation ....................................................................... 71
  5.4. Dispensing ............................................................................... 71
  5.5. Dosage and Administration ...................................................... 71
    5.5.1. Investigational Product: RLY5016 ................................ 71
    5.5.2. Losartan .......................................................................... 72
    5.5.3. Spironolactone ................................................................. 72
  5.6. Drug Accountability ................................................................. 73
5.6.1. RLY5016 ............................................................................................ 73
5.6.2. Losartan and Spironolactone .............................................................. 73
5.7. Assessment of Compliance ........................................................................ 74
5.8. Concomitant Medications ......................................................................... 74
5.8.1. Prohibited Concomitant Medications .................................................. 74
5.8.2. Allowed Concomitant Medications ...................................................... 75
6. STUDY PROCEDURES .............................................................................. 75
6.1. Screening Period ...................................................................................... 76
6.1.1. Study Visit S1 ..................................................................................... 76
6.2. Run-In Period ........................................................................................ 78
6.2.1. Study Visit R0 (3 – 10 Days after S1) .................................................... 78
6.2.2. Study Visit R1 (Day 7±1 from R0), R2 (Day 14±1), and R3 (Day 21±1) 79
6.2.3. Re-screening of Patients ..................................................................... 80
6.3. RLY5016 Treatment Initiation Period ....................................................... 80
6.3.1. Study Visit T0 (Day 1) – Baseline ....................................................... 80
6.3.2. Study Visits T1 to T9 (Days 3 to 57) .................................................... 82
6.3.2.1. Visit T1 (Day 3+1) ....................................................................... 82
6.3.2.2. Visits T2 (Day 8±1), T4 (Day 22±1), T6 (Day 36±1), and T8 (Day 50±1) 83
6.3.2.3. Visits T3 (Day 15±1) and T7 (Day 43±1) ..................................... 83
6.3.2.4. Visit T5 (Day 29±1) ..................................................................... 84
6.3.2.5. Visit T9 (Day 57±1) ..................................................................... 85
6.4. Long-Term Maintenance Period ............................................................... 86
6.4.1. Study Visits M1 (Week 12 ±3 days), M4 (Week 24 ±3 days) and M7 (Week 36 ±3 days) ................................................................. 87
6.4.2. Study Visits M2 (Week 16 ±3 days), M3 (Week 20 ±3 days), M5 (Week 28 ±3 days), M6 (Week 32 ±3 days), M8 (Week 40 ±3 days), M9 (Week 44 ±3 days) and M10 (Week 48 ±3 days) ................................. 88
6.5. End of Treatment or Early Termination (M11/ET Week 52 ± 3days) ....... 89
6.6. Other Visits .......................................................................................... 90
6.6.1. Mandatory Safety Visit .................................................................... 90
6.6.2. Weekly Maintenance Visits (±1day) .................................................... 90
6.6.3. Unscheduled Visit .......................................................................... 91
6.7. Follow-up Period .................................................................................. 91
6.7.1. F1 – F5 Visits .................................................................................... 91
6.7.2. Survival Follow-up Telephone Contact .............................................. 92
7. ASSESSMENT OF EFFICACY AND SAFETY ............................................ 92
7.1. Primary Variables ................................................................................ 92
7.1.1. Treatment Initiation Period Primary Efficacy Variable ...................... 92
7.1.2. Long-Term Maintenance Period Primary Safety Variable ................. 92
7.2. Efficacy Variables.....................................................................................93
  7.2.1. Treatment Initiation Period Secondary Efficacy Variables ............... 93
  7.2.2. Long-Term Maintenance Period Efficacy Variables............................ 94
  7.2.3. Exploratory Measures......................................................................... 94
7.3. Safety Parameters ...................................................................................95
  7.3.1. Adverse Events .................................................................................. 95
  7.3.2. Blood Laboratory Safety Tests ........................................................... 95
  7.3.3. Urinalysis.......................................................................................... 97
  7.3.4. Urine Albumin and Creatinine, Urine Albumin-to-Creatinine Ratio (ACR) 97
  7.3.5. Urine Pregnancy Test......................................................................... 97
  7.3.6. Abnormal Laboratory Tests ............................................................... 97
  7.3.7. Resting Heart Rate and Sitting Blood Pressure.................................. 97
  7.3.8. Physical Examination ....................................................................... 98
  7.3.9. Electrocardiogram (ECG) ................................................................. 98
  7.3.10. Estimated Glomerular Filtration Rate (eGFR).................................... 98
8. ADVERSE EVENT COLLECTION AND REPORTING ...............................99
8.1. Definitions ................................................................................................99
  8.1.1. Definition of Adverse Event (AE) ........................................................ 99
  8.1.2. Definition of Serious Adverse Event (SAE)....................................... 100
8.2. Procedures for Eliciting, Recording and Reporting Adverse Events............101
  8.2.1. Adverse Event Reporting Period ..................................................... 101
  8.2.2. Eliciting Adverse Events ................................................................. 101
  8.2.3. Assessing Adverse Events ............................................................... 101
  8.2.4. Recording Adverse Events .............................................................. 102
8.3. Serious Adverse Events Reporting ..........................................................103
  8.3.1. SAE Notification ............................................................................. 103
  8.3.2. SAE Expedited Reporting ............................................................... 104
8.4. Procedures for Reporting Pregnancy Exposure and Birth Events..............104
9. STATISTICAL METHODS AND DATA ANALYSIS...............................105
9.1. Determination of Sample Size..................................................................105
  9.1.1. Stratum 1......................................................................................... 105
  9.1.2. Stratum 2......................................................................................... 105
9.2. Tests of Hypothesis and Significance Levels ............................................106
9.3. Randomization and Blinding of the Treatment Assignment......................106
9.4. Baseline Comparability ..........................................................................107
  9.4.1. Analysis of Stratum 1 Baseline Data ............................................... 107
  9.4.2. Analysis of Stratum 2 Baseline Data ............................................... 107
9.5. Analysis of Efficacy Data..........................................................................107
  9.5.1. Efficacy Parameters ........................................................................ 108
  9.5.2. Analysis Population and Pooling of Investigators............................. 109
9.5.3. Definition of Baseline and Endpoint Measurements ......................... 109
9.5.4. Methods for the Analysis of Stratum 1 Efficacy Data: ....................... 110
9.5.5. Methods for the Analysis of Stratum 2 Efficacy Data: ....................... 110
9.5.6. Methods for the Analysis of Efficacy Data Collected for the Long-Term Maintenance Period: ........................................................................................................ 111

9.6. Interim Data Analysis .............................................................................111
9.7. Analysis of Safety Data ..........................................................................112

10. REGULATORY AND PROCEDURAL REQUIREMENTS ....................... 113
10.1. Ethical Considerations ......................................................................... 113
10.2. Institutional Review Board/Independent Ethics Committee .......... 113
10.3. Informed Consent ................................................................................ 114
10.4. Data Collection, Verification, and Quality Assurance and Control115
    10.4.1. Source Documentation .................................................................. 115
    10.4.2. Electronic Case Report Forms (eCRFs) ........................................... 115
    10.4.3. Data Collection ............................................................................. 116
    10.4.4. Data Verification .......................................................................... 116
    10.4.5. Data Quality Assurance ................................................................. 117
    10.4.6. Data Quality Control ..................................................................... 117
10.5. Monitoring and Inspections ................................................................. 117
10.6. Protocol Deviations .............................................................................. 118
10.7. Patient Recruitment .............................................................................. 118

11. DATA HANDLING AND RECORDKEEPING ........................................... 118
11.1. Patient Confidentiality ......................................................................... 118
11.2. Recordkeeping and Retention .............................................................. 119
11.3. Financing and Insurance ..................................................................... 119
11.4. Publication Policy ................................................................................ 119

12. REFERENCES ..........................................................................................120
APPENDIX A Schedule of Events ................................................................. 124
APPENDIX B Listing of Laboratory Assays ................................................... 128
APPENDIX C RLY5016 Treatment Initiation Titration Flowchart
    (Visits T0 – T1)................................................................................................. 129
APPENDIX D RLY5016 Treatment Initiation Titration Flowchart
    (Visits T2 – T8)................................................................................................. 130
APPENDIX E RLY5016 Long-Term Maintenance Titration Flowchart
    (Visits T9 – week 51)....................................................................................... 131
APPENDIX F End of Treatment / Early Termination Flowchart............... 133
# Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>ACEI(s)</td>
<td>Angiotensin-converting enzyme inhibitor(s)</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin to creatinine ratio</td>
</tr>
<tr>
<td>ADMA</td>
<td>Asymmetric dimethylarginine</td>
</tr>
<tr>
<td>ADME</td>
<td>Absorption, distribution, metabolism, and excretion</td>
</tr>
<tr>
<td>AE(s)</td>
<td>Adverse event(s)</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>apoA-IV</td>
<td>Apolipoprotein A-IV</td>
</tr>
<tr>
<td>ARB(s)</td>
<td>Angiotensin II receptor blocker(s)</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BID</td>
<td>Two times daily</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type (or brain) natriuretic peptide</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic kidney disease epidemiology collaboration</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Creatine kinase isoenzyme MB</td>
</tr>
<tr>
<td>CRF/eCRF</td>
<td>Case report form/electronic case report form</td>
</tr>
<tr>
<td>CT-proAVP</td>
<td>C-terminal provasopressin</td>
</tr>
<tr>
<td>CT-proET-1</td>
<td>C-terminal pro-endothelin-1</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>eGFR/GFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>ET</td>
<td>Early termination</td>
</tr>
<tr>
<td>FGF23</td>
<td>Fibroblast growth factor 23</td>
</tr>
</tbody>
</table>
GCP | Good Clinical Practice  
g/d | Grams per day  
g/kg/d | Grams per kilogram per day  
HbA1c | Hemoglobin A1c  
HF | Heart failure  
ICF | Informed consent form  
ICH | International Conference on Harmonisation  
IEC | Independent Ethics Committee  
IRB | Institutional Review Board  
IXRS | Interactive Voice or Web Response System  
K⁺ | Potassium  
KIM-1 | Kidney injury molecule 1  
MDRD | Modification of Diet in Renal Disease  
mEq/L | Milliequivalents per liter  
mg/d | Milligrams per day  
mg/dL | Milligrams per deciliter  
mmHg | Millimeters of mercury  
MR-proADM | Midregional pro-adrenomedullin  
MR-proANP | Midregional pro-atrial natriuretic peptide  
NGAL | Neutrophil gelatinase-associated lipocalin  
NOAEL | No observed adverse effect level  
NSAID(s) | Non-steroidal anti-inflammatory drug(s)  
NYHA | New York Heart Association  
PTH | Parathyroid hormone  
QD | Once a day  
QRS | QRS interval (ECG)  
RAAS | Renin angiotensin aldosterone system  
SAE(s) | Serious adverse event(s)  
SBP | Systolic blood pressure  
TID | Three times a day  
T2DM | Type 2 diabetes mellitus
US          United States
USRDS       United States Renal Data System
1. INTRODUCTION AND RATIONALE

1.1. Background

Potassium is an essential dietary mineral that is the main intracellular cation required for membrane activation, ion and solute transport, and the regulation of cell volume. As such, the precise control of potassium homeostasis is critical. Since elevated serum potassium (hyperkalemia) can directly and immediately result in life-threatening arrhythmias, treating or preventing increased serum potassium is a clinically relevant goal. An additional benefit of effective hyperkalemia management is a lower serum potassium level that allows physicians to initiate or maintain optimal therapy with renin angiotensin aldosterone system (RAAS) inhibitors. RAAS inhibitors are proven to reduce the risk of cardiovascular morbidity and mortality [1, 2] and slow the progression of chronic kidney disease (CKD) [3-6], but often result in treatment-limiting hyperkalemia [7].

An elevation in the plasma (extracellular) potassium concentration decreases the ratio of intracellular to extracellular potassium, leading to partial depolarization of the cell membrane. These physiologic effects of hyperkalemia can cause muscle weakness, paralysis and life-threatening effects on cardiac conduction (e.g., QRS widening); arrhythmias such as ventricular fibrillation; and sudden death [8].

Hyperkalemia usually occurs in patients with compromised renal excretion of potassium, arising from impaired kidney function and/or the use of drugs that inhibit renal potassium excretion particularly drugs that interfere with RAAS. It has been shown that patients with glomerular filtration rates (GFRs) lower than 50 mL/min/1.73m² have higher rates of hyperkalemia [2, 9, 10]. Other risk factors for hyperkalemia include diabetes mellitus and older age [10].

High doses of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), commonly referred to as “renoprotective doses”, are recommended as first line treatment for diabetic nephropathy with or without hypertension by the Kidney Disease Outcomes Quality Initiative Guidelines [11], the Seventh Report of the Joint National Committee on High Blood Pressure guidelines.
Protocol RLY5016-205

and Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and of the European Society of Cardiology [13] based on demonstrated benefits in cardiovascular and microvascular parameters. A sub-analysis of the HOPE study [14] in normotensive and hypertensive diabetic patients showed a 25% reduction in combined myocardial infarction, stroke and death due to cardiovascular disease in patients treated with ACEIs vs. placebo added to standard treatment. With respect to microvascular benefits, AVOID [4], RENAAL [5] and IDNT [6] among other studies [15] have demonstrated that high doses or combinations of direct renin inhibitors, ACEIs or ARBs, reduced albuminuria and delayed GFR deterioration. These drugs act to reduce aldosterone production but do not block aldosterone interaction with aldosterone receptor in target cells such as collecting duct cells of the kidney. In fact, some patients may not sustain aldosterone suppression after long term treatment with ACEI or ARB drugs [15], a phenomenon known as aldosterone breakthrough [16]. Since aldosterone promotes tissue inflammation, which can lead to further renal injury and fibrosis [17], the use of direct aldosterone antagonists, such as spironolactone, has demonstrated increased antihypertensive and antiproteinuric benefits in patients receiving ACEI or ARB drugs [15,18].

The use of ACEI or ARB drugs with demonstrated antihypertensive and renoprotective benefits is often associated with an increased risk of hyperkalemia. Captopril (e.g., Capoten®) [19, 20], losartan (e.g., Cozaar®) [21, 22], and irbesartan (e.g., Avapro®, Aprovel®) [23, 24] are approved in the US and EU for the treatment of renal disease in patients with hypertension and/or diabetes. Concerns regarding hyperkalemia associated with use of these drugs are reflected in the product labeling. For example, the US Package Insert (PI) for irbesartan reports an 18.6% rate of serum K+ > 6.0 mEq/L in type 2 diabetes mellitus (T2DM) patients with nephropathy [23]. In addition, hyperkalemia or an increase in serum potassium is listed in the product labeling as a precaution for patients with diabetes and renal impairment for captopril, losartan, and irbesartan [19-22, 24]. Similarly, the prescribing information for spironolactone (Aldactone®) [25, 26] provides specific dosing instructions, warnings, and/or precautions for the management of
hyperkalemia and co-administration with ACEI or ARB therapy. 

Current options for chronic management of hyperkalemia in CKD patients include dietary potassium restriction, use of potassium-wasting diuretics in patients with hypertension or volume overload, and oral bicarbonate in acidotic patients. However, the effectiveness of these treatment options is limited. Dietary potassium restriction is difficult due to the ubiquitous presence of potassium in foods. Because fat, carbohydrates (in diabetics), sodium, and phosphorus tend to be restricted in CKD patients, the addition of a potassium restriction results in severely limited food options, which results in compliance issues. Diuretics, a mainstay for managing sodium, water balance and hypertension, are highly efficient at removing potassium in patients with normal renal function; however, the effectiveness of these drugs is greatly diminished in patients with CKD. The effectiveness of oral sodium bicarbonate is controversial and may only be indicated in patients with hyperkalemia combined with severe acidosis [27].

Sodium polystyrene sulfonate (Kayexalate®) and calcium polystyrene sulfonate (Calcium Resonium®) are cation exchange resins indicated for the treatment of hyperkalemia [28, 29]. Nausea, vomiting, anorexia, constipation, and fecal impaction are common gastrointestinal side effects of Kayexalate or Calcium Resonium. The warnings section of the product labeling of both Kayexalate and Calcium Resonium recommends against concomitant use of sorbitol due to serious complications such as intestinal necrosis [29, 30] and intestinal obstruction [31] which have been reported with the concomitant use of sorbitol. There is also an important concern that Kayexalate is not effective in lowering serum potassium levels unless accompanied by osmotically-active amounts of sorbitol or mannitol [32, 33] and recently, an article has questioned whether Kayexalate is effective in lowering serum potassium [33]. Furthermore, intestinal reabsorption of sodium during Kayexalate treatment can aggravate hypertension and fluid retention. Due to these practical and safety issues, Kayexalate or Calcium Resonium may not be an appropriate therapy for the chronic treatment of hyperkalemia [33].
RLY5016 is a cation binding polymer with approximately twice the total binding capacity for potassium of Kayexalate. Unlike Kayexalate, the exchange cation for RLY5016 is calcium and not sodium; therefore, risks related to aggravation of volume overload and hypertension are removed. Moreover, RLY5016 does not require co-administration with a laxative, which may lead to a better gastrointestinal tolerability profile compared to Kayexalate or Calcium Resonium and may enable RLY5016 use in the chronic treatment of hyperkalemia.

1.2. Description of Investigational Product

RLY5016 is a non-absorbed polymeric drug designed for the binding and removal of potassium from the gastrointestinal tract. RLY5016 is being developed for the treatment of hyperkalemia.

1.3. Summary of Nonclinical and Clinical Experience

Nonclinical pharmacology data demonstrate that RLY5016 binds potassium in simple and complex environments, including ex vivo human aspirates and in vivo animal models. Nonclinical safety data showed that RLY5016 was not genotoxic, was not absorbed from the intestinal tract of rats or dogs, and was not associated with adverse toxicity in rats or dogs after 26 or 39 weeks of dosing, respectively. RLY5016 has been shown to increase fecal potassium excretion in two Phase 1 clinical studies involving 45 healthy subjects and to decrease serum potassium in a Phase 2a study conducted in 6 hemodialysis patients with hyperkalemia. In a Phase 2 placebo-controlled study involving 105 heart failure (HF) patients initiating spironolactone therapy, significantly more HF patients on RLY5016 were able to tolerate increased spironolactone doses compared to placebo patients, and significantly fewer patients on RLY5016 than on placebo developed hyperkalemia. In a subsequent Phase 2 open-label, dose titration study in 63 patients with HF and CKD, RLY5016 allowed spironolactone initiation and up-titration with maintenance of serum potassium in the normal range over the 8 weeks of treatment. A subset of 21 patients with diabetes and urine albumin to creatinine ratio (ACR) ≥ 30 mg/g showed significant reduction in mean blood pressure and albuminuria (p < 0.05) at week 8, suggesting that RLY5016 may allow for the use of beneficial therapy in these high
risk patients.

In the five clinical studies described above, RLY5016 was generally safe and well tolerated at doses ranging from 10 g/day (g/d) to 60 g/d in healthy subjects and the patient populations tested. In addition, these data suggest that RLY5016 may be an effective, non-absorbed potassium binding polymer for the treatment of hyperkalemia.

An overview of the nonclinical studies and the available data from clinical trials conducted with RLY5016 is provided below. Please refer to the Investigator’s Brochure for a more detailed summary of these studies [34].

1.3.1. Nonclinical Pharmacology

RLY5016 was evaluated in vivo using rats and pigs with normal renal function, and in a rat model of chronic renal failure with associated hyperkalemia. In rats with normal renal function, RLY5016 significantly increased the levels of potassium excretion in the feces. In pigs with normal renal function, RLY5016 significantly decreased the levels of potassium excretion in the urine and increased the levels of potassium excretion in the feces. In a rat model of hyperkalemia, RLY5016 treatment significantly reduced serum potassium levels and maintained these levels in the normal range.

1.3.2. Nonclinical Safety

The nonclinical toxicology program conducted for RLY5016 consisted of the following studies: genetic toxicology; safety pharmacology; mammalian toxicology; reproductive toxicology; and absorption, distribution, metabolism, and excretion (ADME) studies.

Results of in vitro and in vivo genetic toxicology studies (Salmonella typhimurium and Escherichia Coli reverse mutation assay, in vitro study in Chinese hamster ovary cells, and in vivo rat micronucleus study) indicated no genotoxic effects of RLY5016 at doses up to 6 g/kg.
A series of four safety pharmacology studies were conducted with an oral administration of RLY5016 at doses up to 6 g/kg in rats, or 3.5 g/kg in dogs. Results of these studies indicated no adverse effects in any of the safety parameters tested but revealed an inhibitory effect on stomach emptying in the rat.

Mammalian toxicology was assessed in the rat and dog. For each species, a dose range-finding study was conducted followed by a 4-week study. Results of these short-term studies indicated no adverse effects or abnormal pathology findings (gross or microscopic) in either species with the no-observed-adverse-effect level (NOAEL) at > 15 g/kg/day and > 7 g/kg/day in the rat and dog, respectively. In addition, two long-term toxicity studies were conducted: a 26-week study in rats and 39-week study in dogs. The results of long-term toxicity studies indicated no adverse effects or abnormal pathology findings (gross or microscopic) in either species with the NOAEL at > 5 g/kg/day and 3.75 g/kg/day in the rat and dog, respectively.

Maternal and embryo/fetal toxicity and teratogenic potential of RLY5016 were evaluated in rats and rabbits. No RLY5016-related toxicity was observed in dams or their litters at oral doses up to 6 g/kg/day in rats or 3 g/kg/day in rabbits, which were the maximum doses studied.

In addition, the effects of RLY5016 on male and female fertility were studied in rats. No adverse effects on fertility were observed at 5 g/kg/day, the highest dose studied.

Systemic absorption was assessed in the rat and dog by a single administration of $^{14}$C-RLY5016. These studies demonstrated that radioactivity was limited to the gastrointestinal tract with only trace amounts of the radio-labeled dose observed in the plasma or urine.

There are no human drug-drug interaction data available for RLY5016. However, RLY5016 has been examined in rat drug-drug interaction studies. Representative examples from several classes of drugs that are commonly co-administered in patients with hyperkalemia were evaluated. In rats, the bioavailability of valsartan
and rosiglitazone was decreased by approximately 30% when co-administered with RLY5016, while the bioavailability of enalapril, quinapril, lisinopril, ramipril, losartan, irbesartan, metoprolol, verapamil, digoxin, glipizide, warfarin, atorvastatin, furosemide, spironolactone, eplerenone, and trimethoprim in rats was not affected by the co-administration of RLY5016.

It is recommended that if a change in serum levels of a concomitantly taken drug would have a clinically significant effect on its safety or efficacy, the drug should be taken at least 1 hour before or 3 hours after administration of RLY5016.

See the Investigator’s Brochure for further information on the nonclinical experience with RLY5016 [34].

1.3.3. **Clinical Experience**

To date five clinical studies of RLY5016 have been completed:

- two Phase 1 studies in healthy subjects (RLY5016-101 and RLY5016-102)
- one Phase 2a study in hyperkalemic hemodialysis patients (RLY5016-201)
- one Phase 2 study in HF patients including a subset with CKD (RLY5016-202)
- one Phase 2 study in CKD with HF patients (RLY5016-204).

1.3.3.1. **Phase 1 Studies in Healthy Subjects (RLY5016-101 and RLY5016-102)**

In the first Phase 1 study RLY5016-101 (double-blind, randomized, parallel-group design) thirty-three healthy adult subjects (26 male and 7 female) received single and multiple doses of RLY5016 or placebo. Patients received a potassium, magnesium, calcium, and sodium cation-controlled diet for the duration of the study. Eight subjects were enrolled in each of the four ascending dose cohorts and were randomly assigned to receive RLY5016 or matching placebo in a 3:1 ratio. The subjects received 1, 5, 10, or 20 g of RLY5016 or placebo as a single dose on study Day 1, followed by three times daily dosing for eight days during study Days 12-19 (3, 15, 30, or 60 g/d of RLY5016 or placebo). RLY5016 caused a significant dose-dependent increase in fecal potassium excretion, with a corresponding decrease in
urinary potassium excretion. There was no change in serum potassium. No early discontinuations due to adverse events (AEs) occurred in RLY5016-treated subjects and no serious adverse events were reported. Adverse events were mild to moderate in severity. There was no apparent dose response relationship with AE reporting, and no increased AE incidence versus placebo. The most frequently reported adverse events in the RLY5016 treatment subjects were gastrointestinal symptoms, which included flatulence, abdominal pain, and diarrhea.

The pharmacology, safety, and tolerability of RLY5016 were further evaluated in the second Phase 1 study RLY5016-102 (open-label, multiple-dose, crossover design). Twelve healthy adult subjects (9 male and 3 female) received 30 g/d RLY5016 for a total of 18 days in QD, BID, and TID dosing regimens. Pharmacology results showed a significant increase in fecal potassium excretion ranging from 1283 to 1550 mg/day (mg/d) on average and concomitant decrease in urinary potassium excretion ranging from 1438 to 1534 mg/d on average across the QD/BID/TID dosing regimens, without a statistically significant difference among the dosing regimens ($p = 0.37$). Comparable effects on fecal potassium excretion and concomitant decrease in urinary potassium excretion were observed with RLY5016 TID, BID, and QD dosing. No early discontinuations occurred, and no serious adverse events were reported. Nine subjects (75%) experienced at least one adverse event. All AEs reported were mild to moderate in severity. Gastrointestinal symptoms reported in three subjects during the BID and QD treatment periods consisted of abdominal pain, constipation, flatulence, and vomiting.

### 1.3.3.2. Phase 2a Study in Hemodialysis Patients (RLY5016-201)

Six hyperkalemic hemodialysis patients (5 male and 1 female) with a mean age of 50 years participated in the Phase 2a study RLY5016-201 (open-label, multiple dose design) to evaluate the pharmacology, safety, and tolerability of RLY5016. Following a 7-day baseline period, patients received 15 g/d RLY5016 (administered as 5 g TID) for a total of 7 days. All patients received a potassium, magnesium, calcium and sodium cation-controlled diet throughout the duration of the study. 
Pharmacology data showed that treatment with 15 g/d RLY5016 (administered as 5 g TID) resulted in a mean decrease in daily serum K+ of 0.4 mEq/L (p = 0.08) and significantly increased fecal potassium excretion by 359 ± 277 mg/d (p = 0.02). Reduction in serum potassium was observed at 24 hours after starting RLY5016 dosing (p = 0.095). In addition, the number of days that patients had serum K+ levels ≤ 5.5 mEq/L increased during treatment relative to the baseline period (67% versus 36%). No early discontinuations occurred, and no serious adverse events were reported. Three patients experienced adverse events during the baseline period, while two patients experienced AEs during the treatment period. AEs considered to be drug-related were nausea and abdominal rigidity (in one patient), which were mild to moderate in severity.

1.3.3.3. Phase 2 Placebo-Controlled Study in Heart Failure Patients (RLY5016-202)

One-hundred-five patients (63 male and 42 female) with a mean age of 68 years participated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of RLY5016 in heart failure patients initiating spironolactone therapy (PEARL-HF) [35]. Patients were randomized to 28 days of treatment with 30 g/d (administered as 15 g BID) RLY5016 (n = 56) or placebo (n = 49). All patients were started on 25 mg/d spironolactone, and those whose serum potassium remained within the normal range were titrated up to 50 mg/d spironolactone after 14 days of treatment.

There was a statistically significant difference in the decrease from baseline in serum K+ of 0.45 mEq/L (p < 0.001) between RLY5016 versus placebo patients. In addition, fewer RLY5016-treated patients compared with placebo patients experienced hyperkalemia defined as serum K+ > 5.5 mEq/L (7% versus 25%, respectively; p = 0.015). In a subset of patients with CKD (eGFR < 60 mL/min, n = 28), the difference in serum K+ between groups was −0.52 mEq/L (p = 0.031), and the incidence of hyperkalemia was 6.7% RLY5016 versus 38.5% placebo (p = 0.041) [35]. There was a statistically significant difference in response between treatment groups at every measured time point, starting at day 3 (2 days after
initiation of study medication). Additionally, more RLY5016-treated patients were able to titrate up to 50 mg spironolactone compared with placebo (91% versus 74%, respectively; \( p = 0.019 \)). No placebo patients in PEARL-HF developed serum \( K^+ > 6.0 \) mEq/L after initiating spironolactone therapy or up-titrating spironolactone to 50 mg/d. Three subjects (5%) on 30 g/d RLY5016 developed serum \( K^+ < 3.5 \) mEq/L that returned to normal after study end (n=1) or discontinuation (n=2).

Although mean serum magnesium values were within normal limits, a small but statistically significant decrease from baseline was observed (−0.22 versus 0.01 mg/dL for the RLY5016 and placebo groups respectively, \( p < 0.001 \)). Hypomagnesemia (serum magnesium < 1.8 mg/dL) occurred in thirteen (24%) RLY5016-treated patients and in one (2.1%) placebo-treated patient. There were no clinically meaningful changes in serum calcium or other laboratory parameters, vital signs, or ECGs.

The incidence of adverse events was higher in the RLY5016 than in the placebo group (53.6% vs. 30.6%, respectively), mostly at the expense of gastrointestinal symptoms, which were experienced by 21% vs. 6% of the patients in RLY5016 vs. placebo group, respectively. The reported gastrointestinal-related AEs in RLY5016-treated patients included flatulence (7%), constipation (5%), diarrhea (5%), and vomiting (4%). Diarrhea was also reported in 2% of placebo patients. Non-serious AEs were reported as mild to moderate, with the exception of one severe case of flatulence, which resolved with treatment discontinuation. Early discontinuation due to adverse events was similar between groups (7.1% for RLY5016 and 6.1% for placebo). Four subjects experienced serious adverse events (SAEs): two in the RLY5016 group (acute myocardial infarction and atrial fibrillation) and two in the placebo group (sudden cardiac death and knee gout). None of the SAEs were considered to be study drug-related by the Investigators.

1.3.3.4. Phase 2 Dose Titration Study in Heart Failure and Chronic Kidney Disease Patients (RLY5016-204)

Sixty-three patients (39 male and 24 female) with a mean age of 71 years
Protocol RLY5016-205 participated in a multicenter, open-label, single arm, dose titration study to evaluate the feasibility of individualized titration of RLY5016 according to serum potassium. Patients on one or more HF therapies (ACEIs, ARBs, or beta-blockers) with a mean baseline serum K+ of 4.8 mEq/L and eGFR of 46 mL/min/1.73m² were started on spironolactone 25 mg/d, which was up-titrated to 50 mg/d if serum K+ was < 5.1 mEq/L. Simultaneously, RLY5016 treatment at 20 g/d was initiated with up- or down-titration allowed in 10 g/d increments from 0 – 60 g/d with the aim of keeping serum K+ in the target range of 4.0 – 5.1 mEq/L, in order to maintain serum K+ in the normal range of 3.5 – 5.5 mEq/L (primary endpoint) during the 8 week treatment period. All patients were up-titrated to spironolactone 50 mg/d by Day 14. Fifty-seven patients (90%) had serum potassium in the normal range at the end of treatment and forty-eight patients (76%) maintained serum potassium in the normal range throughout the entire treatment period. One patient was withdrawn from the study due to hyperkalemia and no patients were withdrawn due to hypokalemia. RLY5016 was titrated 0, 1, and ≥ 2 times in 32%, 21%, and 47% patients, respectively, over 8 weeks. The mean final on-treatment RLY5016 dose was 24 g/d and the maximum dose was 50 g/d. At the last on-treatment visit, 19%, 44%, 18% and 14% of the patients were on 10, 20, 30 and 40 g/d of RLY5016, respectively. Throughout the study, more than 95% of the patients were on doses from 10 to 40 g/d. In a subset of 21 patients with diabetes and urine ACR ≥ 30 mg/g (mean ACR 1107 mg/g), mean blood pressure was reduced from 139/84 at baseline to 129/78 mmHg (p < 0.05), and mean ACR from 1107 to 577 mg/g (p < 0.05) at week 8. Hypomagnesemia (serum magnesium < 1.8 mg/dL) occurred in 8/63 (13%) of patients. There were no clinically meaningful changes in serum calcium or other laboratory parameters, vital signs, or ECGs.

Thirty-six of the 63 patients (57%) experienced at least one AE during the study. Gastrointestinal AEs were the most commonly reported (10/63 patients or 16%) including abdominal discomfort (6%), flatulence (5%) and diarrhea (3%). Four patients (6%) were withdrawn due to AE: one due to moderate diarrhea assessed as related to study drug, and three due to acute or chronic renal failure assessed as unrelated to study drug. Six patients reported unrelated SAEs, including one on-
treatment, unwitnessed death that occurred within 24 hours of a serum K⁺ of 4.6 mEq/L. All SAEs were assessed as not related to the study drug.

See the Investigator’s Brochure for further information [34].

1.4. Rationale for Study Design

1.4.1. Rationale for Run-In

Patients who are hyperkalemic at screening or at the Initial Run-In Visit (R0) will be randomized to their RLY5016 treatment dose immediately. For the remaining patients, the Run-In Period of up to 4 weeks is intended to allow the Investigators to initiate or optimize RAAS therapy with an ACEI and/or ARB, along with an aldosterone antagonist, to provide additional renoprotection and hypertension control, a strategy often limited by the risk of hyperkalemia.

Losartan was chosen from among the available ACEI and ARB drugs as it is the accepted standard of care and is approved in both the US and the EU for the treatment of renal disease in patients with hypertension and diabetes [21, 22]. Unlike ACE inhibitors, losartan is not associated with cough which may cause a higher number of AE-related discontinuations [36]. Studies suggest that a daily 100 mg dose of losartan (the maximum daily dose per the product labeling) is optimal for renoprotection [5, 37] and blood pressure reduction in patients with type 1 and type 2 diabetes mellitus with nephropathy. Further, it is safe to discontinue ACEI and/or ARB drugs and start losartan at 100 mg/d without a washout or dose titration period [4, 36] for this indication.

The addition of spironolactone to conventional treatment with ACEI and/or ARB is expected to provide further antihypertensive and antiproteinuric benefits, as shown in previous studies [15, 16, 17]. Because patients with CKD are at higher risk of hyperkalemia, spironolactone will be started at 25 mg/d (below recommended starting antihypertensive dose of 50 mg/d) [25] and increased to 50 mg/d in patients who do not attain the blood pressure target of 130/80 mmHg [12] or develop hyperkalemia.
In this study, the spironolactone run-in regimen parallels the first 4 weeks of the placebo-treated patients (including a subset of 13 patients with GFR < 60 mL/min/1.73m²) in the RLY5016-202 study, none of whom developed serum K⁺ ≥ 6.0 mEq/L after initiating spironolactone treatment at 25 mg/d or increasing it to 50 mg/d.

1.4.2. Rationale for RLY5016 Starting Doses

The optimal RLY5016 starting dose(s) and RLY5016 titration regimen to be used in future pivotal studies will be determined from dosing information gathered in this study. The maximum RLY5016 dose of 60 g/d in this study is at least 3.75- to 5-fold lower than the maximum doses administered in repeat dose toxicology studies in dogs and rats, respectively, where the NOAEL was never reached.

The RLY5016 starting doses previously evaluated in patient populations ranged from 15 g/d to 30 g/d. In the Phase 2a study RLY5016-201 (hyperkalemic hemodialysis patients), the RLY5016 dose of 15 g/d (administered as 5 g TID) resulted in a mean serum K⁺ decrease of 0.4 ± 0.44 mEq/L during the treatment week relative to the baseline week. In the Phase 2 study RLY5016-202 (HF patients with CKD), RLY5016-treated patients at 30 g/d (administered as 15 g BID) showed a significant serum K⁺ decrease compared to placebo with a difference between groups of −0.52 mEq/L and p = 0.031. In the Phase 2 study RLY5016-204 (open-label dose titration study in CKD patients with HF), all patients started RLY5016 at 20 g/d with up- or down-titration by 10 g/d based on serum potassium values. The RLY5016 doses ranged from 0 g/d (dose withheld) to 50 g/d during the 8 weeks of treatment. Throughout the RLY5016-204 study, more than 95% of the patients were on doses from 10 to 40 g/d and the most common doses were 20 and 30 g/d. The mean final on-treatment RLY5016 daily dose was 24 g/d.

Therefore, based on results from the RLY5016 clinical studies to date, there is a reasonable probability of observing the desired pharmacologic serum potassium lowering effect with the four RLY5016 starting doses (10, 20, 30, 40 g/d) selected in this study.
1.4.3. Rationale for the Long-Term Maintenance Period

The rationale for the Long-Term Maintenance Period to the AMETHYST-DN trial is to allow assessment of the safety of RLY5016 treatment for up to a total of 12 months, which is the ICH-recommended duration of exposure to demonstrate the safety of long-term treatment [38]. The Long-Term Maintenance Period will also allow assessment of the effect of chronic administration of RLY5016 on maintenance of serum potassium levels within a normal target range and the RLY5016 dose adjustment requirements for maintaining serum potassium levels during long-term treatment. Likewise, benefits of enhanced RAAS blockade may become more apparent over the course of one year of treatment and may provide further confirmation of the value of RLY5016 in treating hyperkalemia, the latter of which is a barrier to optimum RAAS therapy.

1.4.4. Rationale for RLY5016 Dose Titration

In the RLY5016-204 study (CKD population with HF, on background therapy with RAAS inhibitors, beta-blockers, and spironolactone) individualized dose titration with RLY5016 (co-administered with spironolactone) allowed successful maintenance of serum potassium in the target range of 4.0 – 5.1 mEq/L.

Data from the RLY5016-204 study indicate that RLY5016 dose titration up or down by 10 g/d lowers or increases serum potassium, respectively. In that study mean change in local lab serum potassium was -0.48 ± 0.41 mEq/L one week after RLY5016 up-titration and +0.54 ± 0.59 mEq/L one week after RLY5016 down-titration (Figure 1). Furthermore, the mean change in serum potassium after one week of RLY5016 up- or down-titration by 10 g/d appeared to be dose-dependent and the magnitude of serum potassium reduction was greater at higher pre-titration serum potassium values.
In this study, the selected RLY5016 starting doses and the initial 8-week titration regimen are anticipated to both lower serum potassium and successfully stabilize serum potassium within the target range. RLY5016 titration instructions during this period will be provided by IXRS upon entry of the local lab serum potassium value.

Patients continuing in the Long-Term Maintenance Period of the study will be those who responded to RLY5016 treatment in the first 8 weeks. As their serum potassium becomes more stable, it is anticipated that they will require fewer and less frequent dose titrations. Therefore, the dose titration algorithm in the Long-Term Maintenance Period is simplified and the frequency of follow-up visits is reduced, as recommended by the KDOQI guidelines [11], thereby increasing patient convenience while ensuring appropriate safety measures are in place.

1.4.5. **Rationale for Continuation of RAAS Inhibitors after RLY5016 Discontinuation**

In order to assess the effect of the withdrawal of RLY5016 on serum potassium when receiving treatment with RAAS inhibitors, normokalemic patients (serum $K^+ \leq 5.0$ mEq/L) will remain on all RAAS inhibitors for 28 days after RLY5016 discontinuation, returning for 5 follow-up visits F1, F2, F3, F4 and F5 in 3, 7, 14, 21, and 28 days, respectively, after RLY5016 discontinuation. The 28-day follow-up
period is identical in duration to the 28-day Run-In Period. Patients who experience
significant hyperkalemia during the follow-up period will be treated per standard of
care (as judged by the Investigator).

Patients with serum $K^+ > 5.0$ mEq/L at the study end of treatment/ET visit will
discontinue RLY5016, all RAAS inhibitors and will return for the follow-up visits F1
and F2 in 3 and 7 days, respectively, after RLY5016 discontinuation.

1.5. Summary of Known and Potential Benefits and Risks

The benefits of study participation include:

1) The potential benefits of RLY5016 treatment
2) The known benefits of optimal RAAS blockade

The main risks of study participation include:

1) The potential risks of treatment with RLY5016
2) The known risks of the study-mandated treatment with RAAS inhibitors,
   including hyperkalemia (see Section 1.1)
3) The underlying risks of the disease being studied, i.e. diabetic nephropathy

1.5.1. Potential Benefits of Treatment with RLY5016

Since elevated serum potassium (hyperkalemia) can directly and immediately result
in life-threatening arrhythmias and death, introducing a new therapy such as
RLY5016 for treating increased serum potassium is a clinically relevant goal.
Effective hyperkalemia management with RLY5016 may allow physicians to initiate
and/or maintain optimal therapy with renin angiotensin aldosterone system (RAAS)
blockers. RAAS inhibitors are proven to reduce the risk of cardiovascular morbidity
and mortality [1, 2] and slow the progression of chronic kidney disease (CKD) [3-6],
but often result in treatment-limiting hyperkalemia [7].

In patients with serious renal disease due to diabetes, treatment with RAAS
blockade is often lacking. When RAAS inhibitor treatment occurs, it is often done
with suboptimal, unproven doses due to the fear of hyperkalemia or due to a
necessity to decrease the dose of one or more RAAS inhibitors to manage
hyperkalemia. In the RLY5016-202 and RLY5016-204 Phase 2 studies, daily treatment with RLY5016 demonstrated that co-administration of RLY5016 with RAAS blockade can safely and conveniently prevent RAAS-induced hyperkalemia and allow full dose RAAS blockade to continue. Even in these relatively short-term Phase 2 studies (up to 8 weeks in duration), a beneficial effect of the RAAS inhibitor was seen in reducing the level of proteinuria and blood pressure in patients with diabetes and renal disease. In the AMETHYST-DN trial (RLY5016-205), treatment with the oral, non-absorbed cation-exchange polymer RLY5016 with individualized dose titration based on frequent potassium monitoring is expected to effectively control serum potassium levels thereby allowing optimum treatment with RAAS inhibitors for up to one year.

1.5.2. Benefits of Optimal RAAS Blockade

A number of large and well conducted clinical trials have established the benefit of treating patients with diabetic nephropathy with enhanced RAAS suppression, including two pivotal landmark clinical trials, the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Receptor Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy (IDNT) trial. RENAAL demonstrated that treatment with losartan (50 to 100 mg/day) reduced the progression of renal disease in patients with diabetic nephropathy and improved hypertension control [5]. Compared to placebo, losartan treatment reduced the risk of doubling of creatinine by 25% and reduced the risk of end stage renal disease by 28% during an average follow-up of 3.4 years; the average level of proteinuria declined by 35% in the losartan group in the same period. Average blood pressure was reduced from 152/82 to 146/78 mmHg in the losartan group and from 153/82 to 150/80 mmHg in the placebo group (p<0.001) during the first year of treatment. There was no difference in all cause mortality. In the IDNT trial, patients with diabetic nephropathy were treated with irbesartan, 300 mg/d [39]. Compared to placebo, irbesartan treatment reduced the risk of creatinine doubling by 33% and the risk of end stage renal disease by 23%, and decreased blood pressure from 160/87 mm Hg to 140/77 mm Hg. There was no difference in all cause mortality. A
systematic review of a number of smaller trials that studied the addition of aldosterone antagonists such as spironolactone to ACEI or ARB therapy shows that addition of an aldosterone antagonist resulted in an additional 30-40% reduction in proteinuria and decreased the rate of decline in GFR compared to controls [15]. A frequent limitation of the treatment of diabetic nephropathy with enhanced RAAS blockade is the common occurrence of hyperkalemia, which occurs with a frequency of 20-25% in patients receiving double or triple RAAS therapy [7].

1.5.3. Potential Risks of Treatment with RLY5016

As RLY5016 is a high molecular weight polymer, the polymer is not absorbed and does not circulate systemically. Thus, there is little risk of toxicity or idiosyncratic adverse drug reactions due to systemic exposure. RLY5016 has been generally safe and well tolerated in previous clinical studies. Single and multiple doses of RLY5016 up to a total daily dose of 60 g/d were well-tolerated in two Phase 1 healthy subject studies and in three Phase 2 studies, one in hemodialysis patients and two in patients with HF and CKD. The main risk of RLY5016 treatment is an exaggerated pharmacological effect which can result in hypokalemia (serum K+<3.5 mmol/L). Magnesium can also be removed by ion exchange with RLY5016 which can result in hypomagnesemia (serum Mg²⁺<1.8 mg/dL). In the PEARL-HF trial (RLY5016-202), the incidence of hypokalemia was 5% in the 30 g/d RLY5016 fixed dose group compared to 0% of the placebo group (titration of RLY5016 was not allowed). The incidence of hypomagnesemia was 24% in the RLY5016 group and 2% in the placebo group. In the open-label RLY5016-204 trial, the starting dose of RLY5016 was 20 g/d and was titrated at weekly visits according to potassium level. With careful titration and follow-up, only one of 63 patients developed hypokalemia (serum K+<3.5), which was promptly reversed by decreasing the dose of RLY5016. Hypomagnesemia (serum Mg²⁺< 1.8 mg/dL) occurred in 8/63 (13%) of patients. In the current trial, serum magnesium will be monitored on the same schedule as potassium and supplementation with magnesium salts will be given to patients who develop hypomagnesemia.

A small amount of fluoride may be released from RLY5016 due to degradation of the
polymer. Degradation is slowed by refrigeration and has also been addressed by the addition of a stabilizer to the polymer formulation and by optimizing the manufacturing process such that fluoride release is minimized. In the 4-week RLY5016-202 study, a RLY5016 dose of 30 g/d resulted in a mean serum fluoride change from baseline of 3.5 ng/mL, which was not statistically significant compared to placebo (p=0.08). In the 8-week RLY5016-204 study (mean RLY5016 dose of 25.3 g/day), mean serum fluoride levels increased 8.7 ng/mL and 9.4 ng/mL after 4 and 8 weeks, respectively. Serum fluoride levels were similar at 4 and 8 weeks suggesting that fluoride may not accumulate with long-term dosing of RLY5016. The fluoride exposure in any of the clinical studies with RLY5016 was lower than the recommended amount of fluoride used for prevention of dental caries [34] and within the guidelines established by the US and EU Agencies. Serum fluoride will be measured periodically during the trial.

The adverse effects of RLY5016 due to local exposure tend to be limited to the gastrointestinal tract and are usually mild to moderate in severity. The most commonly reported GI symptoms reported by patients in the RLY5016-202 and RLY5016-204 trials include abdominal discomfort or pain, flatulence, diarrhea, constipation, nausea and vomiting. Treatment-related adverse events with other polymer-based drugs (e.g., sevelamer, sodium polystyrene sulfonate, colesevelam) include nausea, vomiting, constipation, diarrhea, flatulence, abdominal pain, dyspepsia, and taste loss. No SAEs in RLY5016 studies were considered related to the investigational product.

1.5.4. Risks of Treatment with RAAS Inhibitors

Treatment of patients with diabetic nephropathy with ACEI, ARB, and aldosterone antagonists (RAAS inhibitors) carries the main risks of acute reduction in GFR, hyperkalemia, and hypotension [19-26]. The initial reduction of GFR when RAAS inhibitors are started is due to attenuation of hyperfiltration in remnant glomeruli, which ultimately protects these glomeruli from further damage and loss during continued treatment [19-26]. Hyperkalemia is a known complication of ACEIs, ARBs, and aldosterone antagonists. The RENAAL and IDNT trials demonstrated the
incidence of hyperkalemia with two angiotensin II receptor antagonists (losartan and irbesartan, respectively). In the RENAAL trial of approximately 1500 Type 2 diabetic nephropathy patients, 26.7% of losartan treated patients (50-100 mg/d) had adverse events of hyperkalemia, compared to 13.1% of the placebo patients [40], and in the IDNT study of approximately 1700 diabetic nephropathy patients, 21.5% of irbesartan treated patients (300 mg/d) had hyperkalemia (serum K+ ≥ 6.0 mEq/L), compared to 7.1% of placebo patients [41]. In the Randomized Aldactone Evaluation Study (RALES), 20% of spironolactone patients receiving a dose of 50 mg/d had hyperkalemia (serum K+ ≥ 5.5 mmol/L), compared to 5% of placebo patients [42]. In the PEARL-HF trial (RLY5016-202), only 7% of RLY5016 treated patients developed hyperkalemia (serum K+ > 5.5 mmol/L) compared with 25% of the placebo patients [35]. Hypotension can occur during treatment with RAAS inhibitors, especially in the presence of volume depletion due to diuretic use or in patients with renal artery stenosis. In the RENAAL study, the incidence of hypotension was 7% in the losartan group (50 to 100 mg/d) and 3% in the placebo group [21]. In the IDNT trial, 5.4% of irbesartan treated patients experienced orthostatic hypotension compared to 3.2% of placebo patients [23].

The risks of RAAS inhibitor treatment in the AMETHYST-DN trial will be controlled by the judicious titration of spironolactone based on blood pressure and potassium level and patients with symptomatic hypotension that persists after spironolactone dose adjustment will be withdrawn from the study. Likewise, patients who develop hyperkalemia that persists after appropriate dose adjustments of RLY5016 and RAAS inhibitors will be withdrawn from the trial and treated by standard of care.

1.5.5. Risks of Diabetic Nephropathy

Diabetes by itself increases both the risk of cardiovascular events as well as end organ damage, including renal injury which can progress to end stage renal failure. Diabetes is the most common cause of end stage renal failure [11] and the risk of cardiovascular events is far worse for diabetics who also have renal disease. According to United Kingdom Prospective Diabetes Study data, as diabetic renal disease progresses to macroalbuminuria, the rate of death (4.6% per annum) is
much greater than the rate of progression to ESRD (2.3%) [43]. In addition to the cardiovascular and renal risks, diabetic patients also face the risks of hyperglycemia and hypoglycemia induced by treatment, as well as other end organ complications such as retinopathy, neuropathy, and peripheral microvascular disease leading to foot ulcers and in severe cases, amputation.

2. **OBJECTIVES**

The primary objective of this study is:

- To determine the optimal starting dose of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone

The secondary objectives of this study are:

- To determine the efficacy of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone
- To determine the safety of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone
- To evaluate the chronic use of RLY5016

3. **STUDY DESIGN**

3.1. **Description**

This is an open-label, randomized, dose ranging study to determine the optimal starting dose, efficacy and safety of RLY5016 in treating hyperkalemia in approximately 300 hypertensive patients with nephropathy due to type 2 diabetes mellitus (T2DM) receiving ACEI and/or ARB drugs, with or without spironolactone.

Upon successful completion of screening evaluations at the Screening Visit (S1):
- **Non-hyperkalemic patients** (local lab serum K⁺ 4.3 – 5.0 mEq/L at S1) will
enter the Run-In Period of up to 4 weeks. At the Initial Run-In Visit (R0) patients with local lab serum K⁺ 4.5 – 5.0 mEq/L will discontinue current ACEI and/or ARB drug and start losartan 100 mg/d (Cohort 1); however, based on Cohorts 1 and/or 3 enrollment data, Cohort 2 may be re-activated (as per the original protocol dated 22 February 2011). Cohort 2 patients will remain on current ACEI and/or ARB drugs and start spironolactone 25 mg/d at the R0 Visit.

- Hyperkalemic patients (confirmed local lab serum K⁺ > 5.0 – < 6.0 mEq/L at S1 or R0) will continue their current ACEI and/or ARB drug dose and any other antihypertensive medication and start RLY5016 treatment (T0) without entering the Run-In Period (Cohort 3).

At the first occurrence of serum K⁺ > 5.0 – < 6.0 mEq/L during the Run-In Period, patients from Cohorts 1 and 2 will be randomized to a starting dose of RLY5016 according to their baseline (T0 Visit) serum potassium value. Patients with baseline serum K⁺ > 5.0 – 5.5 mEq/L will be randomized to either: 10 g/d, 20 g/d, or 30 g/d (1:1:1 ratio) starting dose of RLY5016. Patients with baseline serum K⁺ > 5.5 – < 6.0 mEq/L will be randomized to either: 20 g/d, 30 g/d or 40 g/d (1:1:1 ratio) starting dose of RLY5016.

In Cohort 3, hyperkalemic patients with baseline serum K⁺ > 5.0 – 5.5 mEq/L will be randomized to either: 10 g/d, 20 g/d, or 30 g/d (1:1:1 ratio) starting dose of RLY5016; while hyperkalemic patients with baseline serum K⁺ > 5.5 – < 6.0 mEq/L will be randomized to either: 20 g/d, 30 g/d or 40 g/d (1:1:1 ratio) starting dose of RLY5016.

The study has two RLY5016 treatment periods: a Treatment Initiation Period for 8 weeks, followed by a 44-week Long-Term Maintenance Period which allows treatment with RLY5016 for up to one year. During the Treatment Initiation Period, patients randomized to RLY5016 treatment on Day 1 (T0 Visit) will have study visits scheduled on Days 3, 8, 15, 22, 29, 36, 43, 50, and 57 (T9 or Week 8 Visit). Patients completing the 8-week Treatment Initiation Period will continue in the Long-
Term Maintenance Period with at least 11 scheduled Monthly Visits (M1-M11/ET) four weeks apart. During the Long-Term Maintenance Period visits may occur more frequently if RLY5016 dose adjustment is necessary.

During scheduled study visits, the RLY5016 dose may be adjusted according to the corresponding titration algorithm (see Section 3.5.2 and 3.6.2) designed to maintain an individual's serum potassium value in the target range based on local laboratory data.

Serum potassium will be measured at every study visit and dosing decisions will be based on local lab results. To minimize the variance in serum potassium results, and avoid hemolysis of samples, specimen collection and handling must strictly follow specific instructions provided in the Laboratory Manual. Serum potassium samples (local and central lab) should be collected at approximately the same time in the morning for the same patient at ALL Study Visits (including any Mandatory Safety Visits and any Unscheduled Visits).

After RLY5016 discontinuation and depending on the final serum potassium level, patients will either return for 2 follow-up visits within 1 week (F1 and F2) or 5 follow-up visits within 4 weeks (F1 – F5).

### 3.2. Study Periods

The study consists of the following periods:

- **Screening:** up to 10 days (1 visit: S1)
- **Run-In:** up to 4 weeks (1 to 4 visits: R0 to R3)
- **RLY5016 Treatment Initiation:** first 8 weeks of RLY5016 treatment (a minimum of 10 visits: T0 to T9)
- **Long-Term Maintenance:** additional 44 weeks of RLY5016 treatment up to a total of one year (minimum of 11 additional monthly visits: M1-M11/ET)
- **Follow-up (after RLY5016 Discontinuation):** 1 week (2 visits: F1 and F2) OR 4
weeks (5 visits: F1 to F5) depending on the final serum potassium level. Patients who discontinue from the study will be followed up for survival status (phone calls) from the date of their last follow-up visit up until one year after their Treatment Initiation date (Baseline, T0 Visit)

### 3.3. Screening Period

The screening period (up to 10 days) begins at the screening S1 Visit. Upon completion of screening evaluations:

- Patients with local lab serum K⁺ < 4.3 mEq/L at the S1 Visit will be considered screen failures.

- Patients with local lab serum K⁺ 4.3 – 5.0 mEq/L, \textit{central} lab eGFR 15 – < 60 mL/min/1.73m², ACR ≥ 30 mg/g, SBP > 130 – ≤ 180 mmHg and DBP > 80 – ≤ 110 mmHg, who meet all other eligibility criteria for patients without hyperkalemia, will return for the R0 Visit.

- Patients with local lab serum K⁺ > 5.0 – < 6.0 mEq/L (confirmed by same day re-test from a new blood draw), local lab eGFR 15 – < 60 mL/min/1.73m² (calculated using CKD-EPI or MDRD equation), and who meet all other eligibility criteria for patients with hyperkalemia, will have the Visit S1 converted to Baseline Visit T0 and start RLY5016 treatment at the assigned dose (Cohort 3).

- Patients with local lab serum K⁺ > 6.0 mEq/L (confirmed by same day re-test from a new blood draw) will be considered screen failures and should be managed at the discretion of the Investigator.

### 3.4. Run-In Period

The Run-In Period is intended to provide antihypertensive treatment with ACEI and/or ARB drugs, with or without spironolactone (up to 50 mg/d) until the patient achieves blood pressure control or develops hyperkalemia. At the Initial Run-In Visit (R0):

- Patients with local lab serum K⁺ < 4.5 mEq/L will be considered screen
failures.

- Patients with local lab serum K⁺ 4.5 – 5.0 mEq/L, central lab eGFR 15 – < 60 mL/min/1.73m², average R0 ACR ≥ 30 mg/g, SBP > 130 – ≤ 180 mmHg and DBP > 80 – ≤ 110 mmHg and who meet all other eligibility criteria for patients without hyperkalemia, will begin the Run-In Period Treatment according to the cohort assignment (Cohort 1 or 2).

- Patients with local lab serum K⁺ > 5.0 – < 6.0 mEq/L (confirmed by same day re-test from a new blood draw), central lab eGFR 15 – < 60 mL/min/1.73m², and who meet all other eligibility criteria for patients with hyperkalemia, will have the R0 Visit converted to Baseline T0 Visit and start RLY5016 treatment at the assigned dose (Cohort 3).

- Patients with local lab serum K⁺ ≥ 6.0 mEq/L (confirmed by same day re-test from a new blood draw) will be considered screen failures and should be managed at the discretion of the Investigator.

The duration of the Run-In Period may be up to 4 weeks. The Run-In Period may include 1 to 4 visits. At the Initial Run-In Visit (R0) patients with serum K⁺ 4.5 – 5.0 mEq/L who are taking at least one ACEI or ARB drug will discontinue all ACEI and/or ARB drugs and start losartan 100 mg/d (Cohort 1); however, based on Cohorts 1 and/or 3 enrollment data, Cohort 2 may be re-activated (as per the original study protocol dated 22 February 2011). Cohort 2 patients will remain on current ACEI and/or ARB drugs and start spironolactone 25 mg/d.

Assignment to cohort will be performed using an Interactive Voice/Web Response System (IXRS).

During the Run-In Period in order to control blood pressure, following the initiation of losartan and/or spironolactone, Cohort 1 and 2 patients will be allowed to add or modify non-RAAS inhibitors and antihypertensive drugs that do not affect blood potassium levels (e.g., calcium channel blocker, alpha-blocker, or alpha-2 agonist) per Investigator’s discretion.
At the first occurrence of a local lab serum K⁺ > 5.0 – < 6.0 mEq/L after the R0 Visit (R1 to R3 Visits) in either Cohort 1 or 2, eligible patients will start the RLY5016 Treatment Initiation Period.

Patients who develop serum K⁺ ≥ 6.0 mEq/L at any point during the Run-In Period (after the R0 Visit) will have a repeat serum potassium test as soon as possible on the same day from a new blood draw. If the repeat serum K⁺ is ≥ 6.0 mEq/L the patients will be considered enrollment failures and they must be discontinued from the study and treated per standard of care. These patients cannot be re-screened.

Depending on the Cohort assignment at the R0 Visit the sequence of events during the Run-In Period will differ and patients will continue the Run-In Period as follows:

**Table 1: Run-In Study Visit Schedule**

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Run-In Day</th>
<th>Local Lab Serum K⁺, mEq/L</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>0</td>
<td>&lt; 4.5</td>
<td>Screen failure</td>
</tr>
<tr>
<td></td>
<td>4.5 – 5.0</td>
<td>Discontinue ACEI and/or ARB + start LS 100 mg/d</td>
<td>Continue ACEI and/or ARB + start SP 25 mg/d</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Continue ACEI and/or ARB. Randomize (T0), <strong>Cohort 3 only</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 6.0</td>
<td>Screen failure</td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>7</td>
<td>≤ 5.0</td>
<td>Continue LS 100 mg/d</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
<td>Randomize (T0)</td>
</tr>
<tr>
<td></td>
<td>≥ 6.0</td>
<td>Enrollment failure</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>14</td>
<td>≤ 5.0</td>
<td>SBP &gt; 130 or DBP &gt; 80 mmHg? Yes – start SP 25 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes – start SP 25 mg/d</td>
<td>No – Continue R1 Tx</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
<td>Randomize (T0)</td>
</tr>
<tr>
<td></td>
<td>≥ 6.0</td>
<td>Enrollment Failure</td>
<td></td>
</tr>
<tr>
<td>R3</td>
<td>21</td>
<td>≤ 5.0</td>
<td>SBP &gt; 130 or DBP &gt; 80 mmHg? Yes – start SP up to 50 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes – start SP up to 50 mg/d</td>
<td>No – Continue R2 Tx</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
<td>Randomize (T0)</td>
</tr>
<tr>
<td></td>
<td>≥ 6.0</td>
<td>Enrollment Failure</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>28</td>
<td>≤ 5.0 or ≥ 6.0</td>
<td>Enrollment failure</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0 – &lt; 6.0</td>
<td>Randomize (T0)</td>
<td>Randomize (T0)</td>
</tr>
</tbody>
</table>

BP – Blood pressure; LS – Losartan; SP – Spironolactone; Tx – Treatment

The average ACR value for R0 Visit (R0 ACR) will be calculated using up to 3
available ACR values from: S1 Visit, one day before R0 Visit, and R0 Visit. Patients in Cohorts 1 and 2 with average R0 ACR < 30 mg/g will be considered screen failures and must be discontinued from the study at the R1 Visit. These patients cannot be re-screened.

Patients with serum $K^+ \leq 5.0$ mEq/L at the end of the Run-In Period (T0 Visit) will be considered enrollment failures and cannot be re-screened.

Patients who are screen failures or enrollment failures after the initiation of losartan and/or spironolactone treatment should discontinue study medications and return for one unscheduled visit within 3 to 7 days (see Section 6.6.3). Data collected during this visit will be recorded on applicable visit case report forms (CRFs).

3.5. RLY5016 Treatment Initiation Period

3.5.1. Randomization to the Starting RLY5016 Dose

The Treatment Initiation T0 Visit (Baseline, Day 1) takes place when the patient develops serum $K^+ > 5.0 – < 6.0$ mEq/L during the Run-In Period (Cohorts 1 and 2) OR at either the S1 or the R0 Visit (Cohort 3).

Eligible patients will be assigned to one of two RLY5016 treatment strata:

- **Stratum 1**: Patients with serum $K^+ > 5.0 – 5.5$ mEq/L will be randomized in a 1:1:1 ratio to receive one of the following RLY5016 starting doses within each study cohort:
  - 10 g/d
  - 20 g/d
  - 30 g/d

- **Stratum 2**: Patients with serum $K^+ > 5.5 – < 6.0$ mEq/L will be randomized in a 1:1:1 ratio to receive one of the following RLY5016 starting doses within each study cohort:
  - 20 g/d
  - 30 g/d
  - 40 g/d
After randomization to the starting RLY5016 dose all patients will initiate the treatment with RLY5016 on the evening of the Day 1 visit.

Randomization to RLY5016 doses will be performed using an IXRS.

3.5.2. Treatment Initiation Period Titration Algorithm

Patients start RLY5016 treatment at their assigned dose level on the evening of Day 1 (after T0 Visit). They should continue taking losartan 100 mg/d (with or without spironolactone 25-50 mg/d) OR pre-study ACEI and/or ARB with spironolactone 25-50 mg/d, (as per their Cohort 1 or 2 assignment), as well as any other protocol-allowed antihypertensive therapy. Patients in Cohort 3 will continue their pre-study ACEI and/or ARB.

The starting RLY5016 dose may be titrated at any scheduled study visit beginning on Day 3 and ending on Day 50. The RLY5016 titration algorithm is designed to maintain serum K⁺ in the target range of 4.0 – 5.0 mEq/L.

All RLY5016 titration and discontinuation decisions will be provided by IXRS based on local lab serum potassium measurements (see Appendices C, D and F). If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day.

If at ANY time during the Treatment Initiation Period a patient’s serum K⁺ value reported by the local lab is ≥ 6.2 mEq/L, the serum potassium test must be repeated as soon as possible on the same day from a new blood draw. If repeat serum K⁺ is:

- ≥ 6.2 mEq/L – The patient must be withdrawn from the study* and the Investigator should provide standard of care for hyperkalemia.

- < 6.2 mEq/L – The patient should be treated by adjusting the RLY5016 dose in accordance with this algorithm (see Section 3.5.2.1 and 3.5.2.2).
3.5.2.1. **Day 3 Visit (T1):**

The RLY5016 dose will only be adjusted at this visit if the local lab serum K⁺ value is:

- **5.8 – < 6.2 mEq/L** – RLY5016 dose increase to 60 g/d (first dose should be taken as the evening dose on the same day of the visit). The patient must return for a visit 1 day later for serum potassium re-evaluation. At this return visit, did serum K⁺ decrease by ≥ 0.4 mEq/L from Day 3 visit?
  - **Yes** – No change in 60 g/d dose. The patient should return for next scheduled study visit (Day 8, T2).
  - **No** – The patient must be withdrawn from the study*. The Investigator should provide standard of care for hyperkalemia.

- **< 3.5 mEq/L** – RLY5016 dose decrease to 10 g/d or to 0 g/d if the patient is currently on 10 g/d. The patient must return for a visit 1 day later and if serum K⁺ at this return visit is:
  - **< 3.5 mEq/L** – The patient must be withdrawn from the study* with RLY5016 discontinued. The Investigator should provide standard of care for hypokalemia.
  - **3.5 – < 4.0 mEq/L** – RLY5016 dose decrease to 0 g/d (except for patients already on the minimum dose of 0 g/d, who must be withdrawn from the study**). The patient should return for next scheduled study visit (Day 8, T2).
  - **≥ 4.0 mEq/L** – No change in RLY5016 dose. The patient should return for next scheduled study visit (Day 8, T2).

Refer to Appendices C and F for schematic representation of RLY5016 titration and discontinuation decisions at the T1 Visit.

3.5.2.2. **Day 8 (T2), Day 15 (T3), Day 22 (T4), Day 29 (T5), Day 36 (T6), Day 43 (T7), and Day 50 (T8) Visits:**

If local laboratory serum K⁺ value is within the **4.0 – 5.0 mEq/L** range, no titration of RLY5016 is required and the patient will continue the same RLY5016 dose until the next scheduled study visit.
The RLY5016 dose will only be adjusted if the local laboratory serum K⁺ value is:

- **> 5.5 – < 6.2 mEq/L** – Did serum K⁺ decrease by ≥ 0.4 mEq/L from previous scheduled visit one week ago?
  - **Yes** – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**).
  - **No** – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**). The patient must return for a visit 1, 2, or 3 days later (timing at the Investigator's discretion). At this return visit (1, 2, or 3 days later), did serum K⁺ decrease by ≥ 0.4 mEq/L from previous visit?
    - **Yes** – No change in RLY5016 dose. The patient will return for the next scheduled study visit.
    - **No** – The patient must be withdrawn from the study*.

- **> 5.0 – 5.5 mEq/L** – Did serum K⁺ decrease by ≥ 0.4 mEq/L from previous scheduled visit one week ago?
  - **Yes** – No change in RLY5016 dose.
  - **No** – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**).

- **3.5 – < 4.0 mEq/L** – RLY5016 dose decrease by 10 g/d (except for patients already on the minimum dose of 0 g/d, who must be withdrawn from the study**).

- **< 3.5 mEq/L** – RLY5016 dose decrease to 10 g/d or to 0 g/d (if the patient is currently on 10 g/d). The patients who are already on the minimum dose of 0 g/d must be withdrawn from the study**.

If serum K⁺ remains < 3.5 mEq/L for 2 consecutive scheduled visits (one week apart) regardless of RLY5016 dose, patient must be withdrawn from
the study (with RLY5016 discontinued and the patient’s serum potassium treated per Investigator's judgment) and return for the follow-up visits (see Section 3.7).

* Patients discontinued per algorithm should attend follow-up visits (see Section 3.7).

** At any of the following Study Visits: T2, T3, T4, T5, T6, T7, T8, and T9 patients who are already on either the maximum RLY5016 dose of 60 g/d or the minimum dose of 0 g/d (no RLY5016 dispensed), AND who meet serum potassium criteria for RLY5016 dose increase or decrease, respectively, must be withdrawn from the study. The Investigator should provide standard of care and the patient should return for the follow-up visits (see Section 3.7).

Refer to Appendices C, D, and F for schematic representation of RLY5016 titration and discontinuation decisions during the Treatment Initiation Period.

3.5.3. Treatment Initiation Period – Per-Protocol Concomitant Medications

3.5.3.1. Losartan:
Patients who receive losartan 100 mg/d (Cohort 1) at the R0 Visit will continue this regimen throughout the entire Run-In and Treatment Initiation Period.

3.5.3.2. ACEI/ARB drugs:
Patients who continue on pre-study ACEI and/or ARB drugs at the R0 Visit (Cohort 2) should maintain stable doses throughout the entire Run-In and Treatment Initiation Period.

Patients who continue on pre-study ACEI and/or ARB drugs at the T0 Visit (Cohort 3) should maintain stable doses throughout the entire Treatment Initiation Period.
3.5.3.3. **Spironolactone:**

Patients on spironolactone will continue on the same (T0) dose throughout the entire RLY5016 Treatment Initiation Period. If a patient develops symptomatic hypotension or SBP < 110 mmHg (with or without symptoms) at any time during the study while on spironolactone, the spironolactone dose should be reduced in half: from 50 to 25 mg/d or from 25 mg/d to 25 mg every other day. If after modifying the dose of spironolactone symptomatic hypotension or a SBP < 110 mmHg persists, non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced. Dose of losartan or pre-study ACEI and/or ARB (whichever applies) should remain unchanged. Once blood pressure returns to normal the spironolactone dose may be increased to a maximum dose of 50 mg/d, at the Investigator’s discretion.

3.5.3.4. **Other Antihypertensive Treatment:**

In order to control blood pressure during the Treatment Initiation Period, all patients will be allowed to add or modify non-RAAS inhibitors and antihypertensive drugs that do not affect blood potassium levels (e.g., calcium channel blocker, alpha-blocker, or alpha-2 agonist) per Investigator’s discretion.

If during the Treatment Initiation Period, a patient develops symptomatic hypotension or SBP < 110 mmHg (with or without symptoms), non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced. For those subjects on spironolactone, the spironolactone dose should be modified before the non-RAAS antihypertensive agents are modified, as described in Section 3.5.3.3.

For patients in Cohort 2 and Cohort 3, the dose(s) of pre-study ACEI and/or ARB medication must remain unchanged.

3.6. **Long-Term Maintenance Period**

The Long-Term Maintenance Period starts on Day 57 (T9 or Week 8 Visit) of the Treatment Initiation Period and lasts for 44 weeks until the end of Week 52 or the M11 Visit. Patients will continue treatment with RLY5016 for up to a total of one
year (including the 8 weeks in the Treatment Initiation Period) and will have at a minimum 11 additional monthly visits: M1 to M11.

3.6.1. RLY5016 Stabilization

At the T9 Visit (Day 57) of the Treatment Initiation Period, patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits (occurring after T9) until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule. Titrations at the T9 Visit and all subsequent Weekly and Monthly Maintenance visits will be based on the Long-Term Maintenance titration algorithm.

3.6.2. Long-Term Maintenance Period Titration Algorithm

During the Long-Term Maintenance Period, the RLY5016 dose may be titrated at any scheduled study visit beginning at the T9 Visit (Week 8) and ending on Week 51. RLY5016 titration and discontinuation instructions will be provided by IXRS upon entry of respective local lab serum potassium value based on the long-term maintenance titration algorithm. The RLY5016 long-term maintenance titration algorithm is designed to maintain serum K\(^+\) in the target range of 3.8 – 5.0 mEq/L and will be used starting at the T9 Visit (Week 8) of the Treatment Initiation Period and ending at Week 51. If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day.

At the T9, M1-M10 visits, if the local laboratory serum K\(^+\) value is within the 3.8 – 5.0 mEq/L range, no titration of RLY5016 is required and the patient will continue on the same RLY5016 dose until the next scheduled study visit.

If at ANY time during the study, a patient’s serum K\(^+\) value reported by the local lab is $\geq 6.5$ mEq/L, the serum potassium test must be repeated as soon as possible on the same day from a new blood draw and if repeat serum K\(^+\) is $\geq 6.5$ mEq/L, the patient must be withdrawn from the study and the Investigator...
should provide standard of care for hyperkalemia. The patient should return for the follow-up visits (see Section 3.7).

RLY5016 dose titration at the T9, M1-M10 visits will be based on the following serum K⁺ value ranges:

- \( \geq 6.5 \text{ mEq/L} \) (confirmed by same day re-test) – The patient must be withdrawn from the study* and the Investigator should provide standard of care for hyperkalemia.

- \( 6.0 – < 6.5 \text{ mEq/L} \) – RLY5016 dose increase by 10 g/d or more (per Investigator’s discretion) up to the maximum of 60 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**). ECG must be performed. RAAS inhibitors should be continued at the same dose. The patient must return for mandatory safety visit scheduled 1, 2, or 3 days later (1st visit) AND may require another visit 7 days after the visit when RLY5016 dose was increased (2nd visit).

If at the 1st mandatory safety visit (1, 2 or 3 days later) serum K⁺ is:

- \( \geq 6.5 \text{ mEq/L} \) – the patient must be withdrawn from the study*

- \( 6.0 – < 6.5 \text{ mEq/L} \) – either:
  - No change in RLY5016 dose. Reduce RAAS inhibitor dose and re-check serum potassium at the 2nd visit (7 days after the RLY5016 dose was increased)
  - OR
  - The patient must be withdrawn from the study* and the Investigator should provide standard of care for hyperkalemia.

- \(< 6.0 \text{ mEq/L} \) – No change in RLY5016 dose; no change in RAAS inhibitor dose; patient must attend the 2nd mandatory safety visit.

At the 2\textsuperscript{nd} mandatory safety visit, patients who continue participation in the study must return for Weekly Maintenance Visits and have RLY5016 dose adjustment performed in accordance with this algorithm. Once patients have been on the same dose of RLY5016 for 3 consecutive weekly visits, they may resume the monthly visit schedule.
• **> 5.5 – < 6.0 mEq/L** – RLY5016 dose increase by 10 g/d (except for patients already on the maximum dose of 60 g/d, who must be withdrawn from the study**). Patient should return in 1 week for RLY5016 dose adjustment as needed in accordance with this algorithm.

• **> 5.0 – 5.5 mEq/L** – No change in RLY5016 dose. Patient should return in 1 week. If at that visit serum K⁺ is:
  o **> 5.0 – 5.5 mEq/L** – RLY5016 dose increase by 10 g/d**. Patient should return in 1 week for RLY5016 dose adjustment as needed in accordance with this algorithm.
  o **≤ 5.0 OR > 5.5 mEq/L** – RLY5016 dose adjustment is performed in accordance with this algorithm.

• **3.5 – < 3.8 mEq/L** – No change in RLY5016 dose. Patient should return in 1 week. If at that visit serum K⁺ is:
  o **≥ 3.5 mEq/L** – RLY5016 dose decrease by 10 g/d (except for patients already on the minimum dose of 0 g/d, who must be withdrawn from the study**). Patient should return in 1 week for RLY5016 dose adjustment as needed in accordance with this algorithm.
  o **< 3.5 OR ≥ 3.8 mEq/L** – RLY5016 dose adjustment is performed in accordance with this algorithm.

• **< 3.5 mEq/L** – RLY5016 dose decrease to 0 g/d (except for patients already on the minimum dose of 0 g/d, who must be withdrawn from the study**). ECG must be performed and the patient must return for two mandatory safety visits scheduled 1, 2, or 3 days (1st visit) AND 7 days (2nd visit) after the visit when RLY5016 dose was decreased. If serum K⁺ is:
  o **< 3.5 mEq/L at either visit** – The patient must be withdrawn from the study*. The Investigator should provide standard of care for hypokalemia.
  o **≥ 3.5 mEq/L at both visits** – The patient should continue participation in the study and return for Weekly Maintenance Visits, when RLY5016 dose will be adjusted in accordance with this algorithm. Once patients have been on the same dose RLY5016 for 3 consecutive weekly visits,
they may resume the monthly visit schedule.

- Patients who remain on 0 g/d of RLY5016 for 4 consecutive weekly visits will be discontinued from the study*.

In order to check for any changes in serum potassium levels, patients who experience symptomatic hypotension or SBP < 110 mmHg and whose dose of spironolactone or ACEI/ARB is reduced, or any patients who require modification of RAAS inhibitor background treatment, should return for an unscheduled visit in 1 week. RLY5016 dose adjustment (if necessary) will be performed in accordance with this algorithm. If their serum potassium remains within the target range, they will resume the monthly visit schedule.

* Patients discontinued per the algorithm should attend follow-up visits (see Section 3.7).

** At any study visit, patients who are already on either the maximum RLY5016 dose of 60 g/d or the minimum dose of 0 g/d (no RLY5016 dispensed), AND who meet serum potassium criteria for RLY5016 dose increase or decrease, respectively, must be withdrawn from the study. The Investigator should provide standard of care and the patient should return for the follow-up visits (see Section 3.7).

Refer to Appendices E and F for schematic representation of RLY5016 titration and discontinuation decisions during the Long-Term Maintenance Period.

3.6.3. Long-Term Maintenance Period – Per-Protocol Concomitant Medications

3.6.3.1. Losartan:

Patients who receive losartan 100 mg/d (Cohort 1) at the R0 Visit will continue this regimen throughout the Long-Term Maintenance Period.

3.6.3.2. ACEI/ARB drugs:

Patients who continue on pre-study ACEI and/or ARB drugs at the R0 Visit (Cohort 2) or at the T0 Visit (Cohort 3) may either:
• increase ACEI and/or ARB doses if needed for blood pressure control up to the highest approved dose of the respective ACEI and/or ARB during the Long-Term Maintenance Period, OR

• start a new ACEI and/or ARB drug, which dose(s) can be increased up to maximum approved during the Long-Term Maintenance Period.

3.6.3.3. Spironolactone:

During the Long-Term Maintenance Period, patients may start or maximize spironolactone dose up to 50 mg/d if needed for blood pressure control. If a patient develops symptomatic hypotension or SBP < 110 mmHg at any time during the study while on spironolactone, the spironolactone dose should be reduced in half (e.g., from 50 to 25 mg/d or from 25 mg/d to 25 mg every other day). If after modifying the dose of spironolactone, symptomatic hypotension or a SBP < 110 mmHg persists, non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced.

Once blood pressure returns to normal the spironolactone dose may be increased to a maximum dose of 50 mg/d, at the Investigator’s discretion.

3.6.3.4. Other Antihypertensive Treatment:

After the start of the Long-Term Maintenance Period, if additional blood pressure reduction is required in order to achieve target levels (SBP < 130 or DBP < 80 mmHg) according to guidelines, the following sequence of drug changes should be considered:

1) For patients in Cohort 1 on Losartan 100 mg/d alone, an ACEI may be added and increased to the maximum approved dose

2) For patients in Cohort 2 and Cohort 3 either:

   a) the dose of pre-study ACEI and/or ARB should be increased to maximum approved dose(s), OR
   b) a new ACEI and/or ARB should be started and increased to maximum approved dose(s)
3) Spironolactone should be started at 25 mg/d or increased up to 50 mg/d
4) Calcium channel blockers or beta blockers can be added
5) Diuretics should be used for the treatment of volume overload or if additional blood pressure control is necessary

During the Long-Term Maintenance Period, if the SBP is > 160 mmHg or DBP > 100 mmHg, and changes are made to the patient's antihypertensive treatment, the Investigator should bring the patient back for a blood pressure check within 1 to 2 weeks.

3.7. Follow-up Period

There are 2 different follow-up schedules which will depend on final local lab serum potassium level. Patients will either return for 2 visits (at 3 and 7 days) or for 5 visits (at 3, 7, 14, 21, and 28 days) after RLY5016 discontinuation. The treatment discontinuation rules for entry in the Follow-up Period are as follows (see Appendix F):

At the End of RLY5016 Treatment or at the Early Termination Visit (any time after T0 to M11/ET Visit):

- Patients with final local lab serum K⁺ ≤ 5.0 mEq/L will discontinue RLY5016 but continue all RAAS inhibitors for 28 additional days, and will return for 5 follow-up visits F1, F2, F3, F4, and F5 scheduled in 3, 7, 14, 21, and 28 days, respectively, after RLY5016 discontinuation.

- Patients with final local lab serum K⁺ > 5.0 mEq/L will discontinue RLY5016 and all RAAS inhibitors and will return for the follow-up visits F1 and F2 scheduled in 3 and 7 days, respectively, after RLY5016 discontinuation.

After completion of the final follow-up visit, patients should be treated per standard of care.

For those patients who discontinue from the study, the Follow-up Period will be extended for up to one year post-randomization (T0 Visit). The purpose of the
extended follow-up will be to gather survival data only and will include a telephone follow-up call every 3 months.

3.8. Blinding

This is an open-label study in which the investigational study staff, patients, and the study sponsor will be unblinded to treatment assignment.

3.9. Choice of Study Design

There will be no control arm in this study; all patients will receive open-label active treatment (RLY5016). An open-label study is a commonly used design to evaluate the titration and safety of an investigational product.

4. SELECTION AND WITHDRAWAL OF PATIENTS

All potential study patients will be evaluated based on study eligibility criteria. Note that some inclusion and exclusion criteria for patients with hyperkalemia (who enter the Treatment Initiation Period directly) and patients without hyperkalemia (who do qualify for the Run-In Period) are different.

4.1. Inclusion Criteria

Patients must meet ALL of the following inclusion criteria:

1. Age 30 – 80 years old at screening
2. Type 2 diabetes mellitus (T2DM) diagnosed after age 30 which has been treated with oral medications or insulin for at least one year prior to screening
3. Chronic kidney disease: eGFR 15 – < 60 mL/min/1.73m² at screening based on central lab serum creatinine measurement (except for patients with hyperkalemia at S1, whose eligibility will be assessed based on local lab eGFR value calculated using CKD-EPI or MDRD equation)
4. Urine ACR:
   a) **Cohorts 1 and 2:** urine ACR ≥ 30 mg/g at screening (S1) AND average urine ACR ≥ 30 mg/g at the beginning of Run-In Period (R0) based on up to 3 ACR values obtained starting at S1 and ending at the R0 Visit
   b) **Cohort 3:** not applicable
5. **Local** laboratory serum K⁺ values of:
a) **Cohorts 1 and 2**: 4.3 – 5.0 mEq/L at S1; AND 4.5 – 5.0 mEq/L at R0; AND > 5.0 – < 6.0 mEq/L at randomization to RLY5016 (Baseline, T0 Visit)

b) **Cohort 3**: > 5.0 – < 6.0 mEq/L at S1 OR at R0 after same day confirmation

6. Must be receiving an ACEI and/or ARB for at least 28 days prior to screening

7. Any patient with a history of hypertension must have average SBP > 130 – ≤ 180 mmHg AND average DBP > 80 – ≤ 110 mmHg (sitting) at both screening and R0 (as applicable). While Cohorts 1 and 2 patients must have a diagnosis of hypertension to be enrolled in the study, Cohort 3 patients without a history of hypertension can be enrolled.

8. Females of child-bearing potential must be non-lactating, must have a negative serum pregnancy test at screening, and must have used a highly effective form of contraception for at least 3 months before RLY5016 administration, during the study, and for one month after study completion

9. Provide their written informed consent prior to participation in the study

4.2. **Exclusion Criteria**

Patients must NOT meet ANY of the following exclusion criteria:

1. Type 1 diabetes mellitus

2. Central lab hemoglobin A1c > 12% at S1 (except for Cohort 3 patients who are hyperkalemic at S1)

3. Emergency treatment for T2DM within the last 3 months

4. A confirmed SBP > 180 mmHg or DBP > 110 mmHg at any time during Screening or Run-In Period or at Baseline T0 Visit

5. Central lab serum magnesium < 1.4 mg/dL (< 0.58 mmol/L) at screening (Cohort 3 patients will be evaluated based on local lab serum magnesium measurement)

6. Central lab urine ACR ≥ 10000 mg/g at screening (except for Cohort 3 patients who are hyperkalemic at S1)

7. Confirmed diagnosis or history of renal artery stenosis (unilateral or bilateral)

8. Diabetic gastroparesis

9. Non-diabetic chronic kidney disease

10. History of bowel obstruction, swallowing disorders, severe gastrointestinal disorders or major gastrointestinal surgery (e.g., large bowel resection)

11. Current diagnosis of NYHA Class III or IV heart failure

12. Body mass index (BMI) ≥ 40 kg/m²
13. Any of the following events having occurred within 2 months prior to screening: unstable angina as judged by the Investigator, unresolved acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, transient ischemic attack or stroke, use of any intravenous cardiac medication

14. Prior kidney transplant, or anticipated need for transplant during study participation

15. Active cancer, currently on cancer treatment or history of cancer in the past two years except for non-melanocytic skin cancer which is considered cured

16. History of alcoholism or drug/chemical abuse within 1 year

17. Central lab liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] > 3 times upper limit of normal at S1 (except for Cohort 3 patients with hyperkalemia at S1, who will have local lab ALT and AST)

18. Loop and thiazide diuretics or other antihypertensive medications (calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent) that have not been stable for at least 28 days prior to screening or not anticipated to remain stable during study participation

19. Current use of polymer-based drugs (e.g., sevelamer, sodium polystyrene sulfonate, colesevelam, colestipol, cholestyramine), phosphate binders (e.g., lanthanum carbonate), or other potassium binders, or their anticipated need during study participation

20. Current use of lithium

21. Use of potassium sparing medications, including aldosterone antagonists (e.g., spironolactone), drospirenone, potassium supplements, bicarbonate or baking soda in the last 7 days prior to screening

22. Use of any investigational product within 30 days or 5 half-lives, whichever is longer, prior to screening

23. Inability to consume the investigational product, or, in the opinion of the Investigator, inability to comply with the protocol

24. In the opinion of the Investigator, any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the patient or affect the validity of the trial results

**4.3. Withdrawal Criteria**

Within the provisions of informed consent and good clinical judgment with respect to the patient's safety, every attempt should be made to have patients complete the study. Patients will be informed that they are free to withdraw from the study at any
time. The Investigator and/or the Medical Monitor may exercise his or her medical judgment to terminate a patient’s participation in the study due to clinically significant changes in any clinical or laboratory parameters.

Patients who meet any of the following criteria must be withdrawn from the study and treated as per standard of care by the Investigator:

- An ECG change related to hyper- or hypokalemia (e.g., ventricular arrhythmias, peaked T waves or increased U waves).
- GFR decrease to < 10 mL/min/1.73m² or need for dialysis.
- Symptomatic hypotension or SBP < 110 mmHg (with or without symptoms) that persists after dose of spironolactone has been reduced and/or other non-RAAS inhibitor agents have either been removed or doses have been decreased.
- Confirmed hypertension with either SBP > 180 mmHg or DBP > 110 mmHg (repeated 30 minutes after the initial readings) at any time during the study if the patient is on at least 3 antihypertensive agents
- Serum magnesium < 1.0 mg/dL (< 0.42 mmol/L)
- Urine ACR ≥ 10000 mg/g
- Death (SAE form must be completed).
- Treatment-related SAE (SAE form must be completed).
- Pregnancy (pregnancy form must be completed).
- Patient withdraws consent.
- Serum potassium withdrawal criteria: Per the RLY5016 titration algorithm a patient’s serum potassium result mandates termination from the study and the patient will enter the follow-up visit schedule based on their final serum potassium level.
  - High serum potassium (see Section 3.3, 3.5.2 and 3.6.2). Treatment for high serum potassium should be performed per Investigator’s judgment: the patient’s clinical situation should dictate the treatment procedures to be employed. These include the intravenous administration of calcium gluconate or calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid-acting insulin preparation.
These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate or calcium polystyrene sulfonate may be administered orally or rectally. Persistent hyperkalemia may require dialysis.

- **Low serum potassium** (see Section 3.3, 3.5.2 and 3.6.2). Treatment for low serum potassium should be performed per Investigator’s judgment (e.g., potassium supplementation).

Other reasons for withdrawal may include:

- **Adverse event.**
- **Protocol violation.**
- **Patient non-compliance:** Poor compliance with study treatment or study visits.
- **Investigator’s decision:** (e.g., in the Investigator’s judgment discontinuation is in the patient’s best interest; need for prohibited medication).
- **Patient is lost to follow-up:** The patient did not return for visits and study personnel were unable to contact.
- **Other:** The patient’s participation in the study was terminated for a reason other than those listed above. The Investigator must specify the detailed reason.

In addition, there are a variety of reasons why either the sponsor or a regulatory agency might terminate the study early, in which case all patients would be withdrawn from the study.

Although a patient is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient’s rights. The procedures described for Early Termination (Section 6.5) will be performed if possible. Every effort will be made to contact a patient who fails to attend a Study Visit, or does not respond by telephone, in order to ensure that he/she is in satisfactory health. The Medical Monitor will be immediately informed of removal or early withdrawal of a patient from the study.
5. STUDY TREATMENTS

5.1. Investigational Product: RLY5016

5.1.1. Formulation, Packaging, and Labeling

Investigational product (RLY5016) is stabilized with sorbitol and will be provided as a powder for oral suspension formulated with xanthan gum. RLY5016 will be packaged in sachets (5 grams per sachet) with appropriate labeling. The individual sachets will be assembled as a kit for dispensing.

5.1.2. Storage

RLY5016 must be stored refrigerated (2-8° C) in a secure location.

5.1.3. Preparation

Patients will be instructed to mix RLY5016 with water, cranberry juice, or other appropriate, low-potassium drink or food (e.g., applesauce). Each dose should be individually prepared immediately prior to administration.

Patients will be instructed to avoid taking RLY5016 with potassium-rich food or drinks, such as: banana puree, milk products, orange, prune, or tomato juice. Patients will be instructed to avoid heating RLY5016 (e.g., microwaving) or adding it to heated food or liquids.

5.2. Losartan

5.2.1. Formulation, Packaging, and Labeling

Losartan is a marketed product and will be provided and supplied by Relypsa from an approved manufacturer. A more detailed description of this product is provided in the losartan product labeling [21, 22].

5.2.2. Storage

Losartan must be stored according to product labeling in a secure location.
5.2.3. Preparation

Losartan will be provided to patients in tablet form at a dosage of 100 mg per tablet.

5.3. Spironolactone

5.3.1. Formulation, Packaging, and Labeling

Spironolactone is a marketed product and will be provided and supplied by Relypsa from an approved manufacturer. A more detailed description of this product is provided in the spironolactone product labeling [25, 26].

5.3.2. Storage

Spironolactone must be stored according to product labeling in a secure location.

5.3.3. Preparation

Spironolactone will be provided to patients in tablet form at a dosage of 25 mg per tablet.

5.4. Dispensing

The dispensing pharmacist or designated qualified individual will be responsible for dispensing RLY5016, losartan, and spironolactone, and for documenting the date dispensed, medication identifier, and patient identification number on the appropriate drug accountability records at the time of dispensation.

5.5. Dosage and Administration

5.5.1. Investigational Product: RLY5016

Patients will begin taking RLY5016 on the evening of Day 1 (after the T0 Visit). The starting RLY5016 dose will be randomly assigned based on baseline local lab serum potassium and then it may be adjusted based on local lab serum potassium values and according to the corresponding titration algorithm described in Sections 3.5.2 and 3.6.2. If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day. The minimum dose of RLY5016 is 0 g/d (no RLY5016
dispensed) and the maximum dose is 60 g/d. Patients will take the daily dose of RLY5016 orally in equally divided doses twice a day with their regular meals (breakfast and dinner). Meals should be consumed at approximately the same time each day. RLY5016 may be taken for up to one year.

5.5.2. **Losartan**

Losartan will be taken orally once daily in the morning. Losartan treatment will be initiated the next morning following the R0 Visit in patients who receive losartan 100 mg/d (Cohort 1). The dose of losartan must remain at 100 mg/d during the Run-In, Treatment Initiation, Long-Term Maintenance, and Follow-up (if applicable) Periods. Losartan may be taken for up to 60 weeks (including follow-up period) until its discontinuation.

5.5.3. **Spironolactone**

Spironolactone will be taken orally once daily at approximately the same time each day. The spironolactone 25 mg/d treatment may be initiated during the Run-In Period, in which case the first spironolactone dose should be taken the next morning, and may be subsequently increased up to 50 mg/d before the T0 Visit or during the Long-Term Maintenance Period. If the spironolactone dose is adjusted, patients will start the new dose the next morning following the dose adjustment visit. Spironolactone may be taken for up to 60 weeks (including follow-up period) until its discontinuation.

The dose of spironolactone during the RLY5016 Treatment Initiation Period will remain the same as it was at the Baseline T0 Visit, except for those patients who develop symptomatic hypotension or SBP < 110 mmHg at any time during the study while on spironolactone, the spironolactone dose should be reduced in half: from 50 to 25 mg/d or from 25 mg/d to 25 mg every other day. If blood pressure continues to remain uncontrolled, non-RAAS inhibitor antihypertensive treatments should either be removed or their doses reduced. Dose of losartan or pre-study ACEI and or/ARB (whichever applies) should remain unchanged. Once blood pressure returns to normal the spironolactone dose may be increased to a maximum dose of 50 mg/d,
at the Investigator’s discretion.

During the Long-Term Maintenance Period, spironolactone may be started at 25 mg/d or increased up to 50 mg/d (if needed) for blood pressure control.

5.6. Drug Accountability

The Investigator or designee will verify and acknowledge receipt of RLY5016, losartan, and spironolactone. All medication must be stored in a secure area under the proper storage requirements with access restricted to the Investigator or designees. Medication designated for this clinical study must not be taken by any patients other than those enrolled in this specific investigation, and may not be utilized for any laboratory or animal research. All medication dispensed to patients (RLY5016, losartan, and spironolactone) must be accurately recorded on the Drug Accountability Record maintained at the Study Center. Patients should be instructed to return all investigational product, losartan, and spironolactone dispensed to them (including empty containers) at each study visit.

All medication and empty containers will be retained at the site for Study Monitor verification.

5.6.1. RLY5016

Drug accountability for RLY5016 will be performed at each scheduled study visit starting on Day 1 (T0) and ending on the last day of RLY5016 treatment. If the RLY5016 dose is adjusted, patients will start the new dose in the evening of the titration day. The last day of RLY5016 treatment will correspond to the end of treatment (Week 52; M11/ET Visit) or the ET Visit. Patients should be instructed to return all RLY5016 supplies dispensed to them during the study on the last RLY5016 treatment visit.

5.6.2. Losartan and Spironolactone

Drug accountability for losartan and/or spironolactone will be performed at each scheduled study visit starting at the first applicable visit during the Run-In Period and
ending at the end of treatment/ET Visit (for patients with serum K⁺ > 5.0 mEq/L) or at any of the Follow-up Visits (for patients with serum K⁺ ≤ 5.0 mEq/L). Patients should be instructed to return all losartan and/or spironolactone medication dispensed to them.

5.7. Assessment of Compliance

Patient training at the Run-In Visit (R0) and subsequent retraining regarding proper dosing of losartan and/or spironolactone will occur to ensure patient’s compliance.

Patient training at the Baseline T0 (Day 1) Visit and subsequent retraining regarding proper dosing and preparation of RLY5016 will occur to ensure patient’s compliance.

Study staff will assess compliance at every study visit after dispensation to confirm that the patient is taking investigational product, losartan, and spironolactone according to the protocol.

5.8. Concomitant Medications

Concomitant medications information will be collected beginning at the Screening (S1) Visit and continuing for the duration of the study (including ET) until the last study visit.

5.8.1. Prohibited Concomitant Medications

During the Treatment Initiation Period use of ACEI and/or ARB drugs (other than per-protocol losartan) will be prohibited for patients who are assigned to Cohort 1 at the R0 Visit as they must discontinue current ACEI and/or ARB therapy and initiate losartan 100 mg/d treatment. During the Treatment Initiation Period use of new ACEI and/or ARB drugs will be prohibited for patients who are assigned to Cohort 2 at the R0 Visit or Cohort 3 at the T0 Visit.

During the entire study participation use of polymer-based drugs (e.g., sodium polystyrene sulfonate, sevelamer, colesvelam, colestipol, cholestyramine), phosphate binders (e.g., lanthanum carbonate) or potassium binders (other than RLY5016), potassium sparing medications (other than per-protocol spironolactone),
drospirenone, potassium supplements, lithium, bicarbonate or baking soda, and intravenous cardiovascular drugs are not allowed.

5.8.2. **Allowed Concomitant Medications**

Use of ACEI and/or ARB drugs at pre-study doses will be allowed during the study only for patients who are assigned to Cohort 2 and 3. All other antihypertensive drugs are permitted if on a stable dose at least 28 days prior to screening.

Diabetes should be managed according to European Association for the Study of Diabetes and American Diabetes Association standard of care and guidelines [44]. Patients should continue taking their anti-diabetic treatment regimen adjusting dosing as needed for blood glucose control. They should continue on regular doses of other usual medications, including non-steroidal anti-inflammatory drugs (NSAIDs), laxatives, and contraceptives. Medications that the Investigator deems indicated for treatment of any intercurrent illness or a preexisting condition that do not form an exclusion criterion for participation in this study are generally allowed.

There are no human drug-drug interaction data available for RLY5016. Therefore, it is recommended that if a change in serum levels of a concomitantly taken drug would have a clinically significant effect on its safety or efficacy, the drug should be taken at least 1 hour before or 3 hours after administration of RLY5016.

6. **STUDY PROCEDURES**

Please see the Schedule of Events (Appendix A) which summarizes the frequency and timing of the required study assessments.

Laboratory-related eligibility criteria will be based on central lab values with the exception of serum potassium, urine pregnancy test (females of child-bearing potential) and Cohort 3 Screening (S1) eGFR, ALT, and AST which will be based on the local lab values.
The Investigator should base decisions related to serum potassium (e.g., RLY5016 titration) on the local lab values only. Central lab potassium results will be used as supplemental safety information and should not override any decisions made by the Investigator based on local lab serum potassium values.

All ECG and laboratory results (in particular serum potassium) must be reviewed by the Investigator as soon as possible.

To minimize the variance in serum potassium results, and avoid hemolysis of samples, specimen collection and handling must strictly follow specific instructions provided in the Laboratory Manual. Serum potassium samples (local and central lab) should be collected at approximately the same time in the morning for the same patient at all Study Visits and at any Unscheduled Visit.

6.1. Screening Period

Before any study-specific procedures are performed, the patient must receive an explanation of all study procedures and must sign and date an Institutional Review Board or Independent Ethics Committee (IRB/IEC) approved written Informed Consent Form (see Section 10.2 and 10.3 for additional requirements).

6.1.1. Study Visit S1

The timing of the Screening Visit (and all subsequent visits) must take into account planned absences at the research facility and the need for study visits according to the Schedule of Events (see Appendix A).

The patient must be assigned a unique patient identification number.

The following activities will be performed:

- Review of inclusion and exclusion criteria
- Review of medical history
- Demographics
- Physical examination
- Body weight and height
- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
- ALT, AST, and serum creatinine (local lab) only if patient’s serum potassium level meets Cohort 3 eligibility requirements (see below)
- Other central laboratory tests (see Appendix A and B):
  - Serum chemistry panel including serum creatinine and eGFR calculation
  - HbA1c measurement
  - Hematology (CBC)
  - Urinalysis
  - Spot urine albumin-to-creatinine ratio (ACR)
  - Serum pregnancy test (females of child-bearing potential only)
- Patient’s registration in IXRS including entry of a local lab serum potassium value
  - Patients with serum K\(^+\) < 4.3 mEq/L at the S1 Visit who meet all other eligibility criteria will be considered screen failures
  - Patients with serum K\(^+\) 4.3 – 5.0 mEq/L will continue to the R0 Visit.
  - Patients with serum K\(^+\) > 5.0 – < 6.0 mEq/L (confirmed by same day re-test from a new blood draw) who meet all other eligibility criteria will enroll in Cohort 3 and convert the S1 Visit to the T0 Visit. All additional applicable T0 (baseline) assessments must be performed (see Section 6.3.1)
  - Patients with serum K\(^+\) ≥ 6.0 mEq/L (confirmed by same day re-test from a new blood draw) will be considered screen failures and should be managed at the discretion of the Investigator
- Adverse Event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient training regarding ACR collection (patients should be instructed to collect urine specimens from the second morning void) for patients who continue to R0

All screening information shall be reviewed by the Investigator as soon as possible for safety and eligibility.
6.2. Run-In Period

6.2.1. Study Visit R0 (3 – 10 Days after S1)

The urine ACR value for the R0 Visit will represent an average ACR value obtained from samples collected at 3 different time points: at S1 Visit, one day before the R0 Visit, and at the R0 Visit. This average ACR value will be used to determine Cohorts 1 and 2 patients’ eligibility to continue in the Run-In Period based on the requirement of average urine ACR ≥ 30 mg/g at the R0 Visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will be performed:

- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
- Urine ACR (central lab): 2 different samples collected:
  - 1 day before the visit
  - at the visit
- Blood and urine samples for potential biomarker analysis (central lab)
- IXRS entry of a local lab serum potassium value and IXRS
  - Patients with serum K⁺ 4.5 – 5.0 mEq/L will be assigned to either Cohort 1 or Cohort 2 if they continue to qualify
  - Patients with serum K⁺ > 5.0 – < 6.0 mEq/L (confirmed by same day re-test from a new blood draw) who meet all other eligibility criteria will enroll in Cohort 3 and convert the visit R0 to visit T0. All additional applicable T0 (baseline) assessments must be performed (see Section 6.3.1)
  - Patients with serum K⁺ ≥ 6.0 mEq/L on a same day re-test are screen failures and should be managed at the discretion of the Investigator
- Losartan or spironolactone dispensation and patient training (as applicable)
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient retraining regarding ACR collection
6.2.2. Study Visit R1 (Day 7±1 from R0), R2 (Day 14±1), and R3 (Day 21±1)

On Days 7, 14 and 21 of the Run-In Period the patient will present for Visits R1, R2, and R3 (if necessary), respectively. If at any of these Run-In Visits the patient’s serum K⁺ > 5.0 – < 6.0 mEq/L and the patient continues to meet eligibility criteria, the visit will be converted to the Baseline T0 Visit with all additional applicable baseline assessments performed.

The urine ACR value for each of these visits will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will be performed at each of these visits:

- Resting heart rate and sitting blood pressure
- Serum potassium (local and central lab)
- Urine ACR (central lab): 3 different samples collected:
  - 2 days before the visit
  - 1 day before the visit
  - at the visit
- IXRS entry of a local lab serum potassium value
  - If serum K⁺ > 5.0 – < 6.0 mEq/L convert to the T0 Visit (perform the rest of the assessments as per Section 6.3.1)
  - If the local lab serum K⁺ ≥ 6.0, repeat serum potassium test from a new blood draw (patients with serum K⁺ ≥ 6.0 mEq/L on a same day re-test are enrollment failures and should be managed at the discretion of the Investigator)
- Losartan and/or spironolactone dispensation, reconciliation, accountability, and patient retraining (as applicable and needed)
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient retraining regarding
Patients who are screen failures or enrollment failures after the initiation of losartan and/or spironolactone treatment will return for one unscheduled visit within 3 to 7 days (see Section 6.6.3). Data collected during this visit will be recorded on applicable visit CRFs.

6.2.3. Re-screening of Patients

Screen failure patients who meet all study entry criteria except for local lab serum potassium, GFR, or ACR at S1 Visit or local lab serum potassium at R0 Visit can be re-screened at the Investigator’s discretion.

To re-screen a patient:

- Patient must be re-consented
- Patient must receive a new patient identification number
- Patient information must be re-entered into IXRS
- All screening evaluations must be repeated (see Section 6.1)

Re-screening of enrollment failure patients who did not meet serum potassium randomization criterion (> 5.0 – < 6.0 mEq/L) at the T0 Visit is not permitted.

6.3. RLY5016 Treatment Initiation Period

6.3.1. Study Visit T0 (Day 1) – Baseline

For Cohorts 1 and 2: The Initial Treatment Visit (T0 - Baseline) takes place when the patient develops serum K⁺ > 5.0 – < 6.0 mEq/L during run-in.

For Cohort 3: The Initial Treatment Visit (T0 - Baseline) takes place at the S1 or R0 Visit, if patient’s serum K⁺ is > 5.0 – < 6.0 mEq/L after a same day re-test.

Patients completing the Run-In Period with serum K⁺ ≤ 5.0 OR ≥ 6.0 mEq/L at the T0 Visit will be considered enrollment failures and will not continue participation in the study.
Patients in Cohort 3 may have up to three urine ACR samples collected at 3 different time points: screening (spot urine ACR), one day before the visit, and at the visit (if converted from R0). For patients in Cohort 1 and Cohort 2, the urine ACR value for the T0 Visit will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will be performed:

- Review of inclusion and exclusion criteria
- Physical examination
- Body weight
- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
- Urine pregnancy test for females of child-bearing potential (local lab) – must be negative before starting RLY5016 treatment
- Other central laboratory tests (see Appendix A and B)
  - Serum chemistry panel
  - Hematology (CBC)
  - Urinalysis
  - Urine ACR (for patients in Cohorts 1 and 2): 3 different samples collected:
    - 2 days before the visit
    - 1 day before the visit
    - at the visit
  - Serum pregnancy test for females of child-bearing potential only
  - Serum fluoride
  - Blood and urine samples for potential biomarker analysis
- IXRS entry of a local lab serum potassium value and IXRS randomization to the starting RLY5016 dose if patient continues to qualify
- RLY5016 dispensation and patient training: patients must be instructed to start taking RLY5016 on the evening of that day
• Losartan and/or spironolactone reconciliation, dispensation, accountability and patient retraining (as applicable and needed)
• Low potassium diet counseling
• Adverse event assessment
• Concomitant medications assessment

6.3.2. Study Visits T1 to T9 (Days 3 to 57)

From Day 1 through Day 57 inclusive, patients will take RLY5016 two times a day with meals (breakfast and dinner) at approximately the same time every day.

RLY5016 doses may be adjusted during the Treatment Initiation Period according to the titration algorithm (see Section 3.5.2, Appendices C and D). Specific attention should be paid whenever the local lab serum K\(^+\) value during the Treatment Initiation Period is either < 3.5 OR ≥ 6.2 mEq/L (see Section 4.3).

On Days 3, 8, 15, 22, 29, 36, 43, 50, and 57 the patient shall present for Visits T1, T2, T3, T4, T5, T6, T7, T8, and T9 (respectively) as detailed below.

6.3.2.1. Visit T1 (Day 3+1)

The following activities will be performed:

• Resting heart rate and sitting blood pressure
• ECG, 12-lead, resting
• Serum potassium (local and central lab)
  – If the local lab serum K\(^+\) ≥ 6.2, repeat serum potassium test from a new blood draw
• IXRS entry of a local lab serum potassium value
• Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
  – If serum K\(^+\) is either 5.8 – < 6.2 mEq/L OR < 3.5 mEq/L, schedule mandatory, next day safety visit (see Section 6.6.1)
• Losartan and/or spironolactone accountability and patient retraining (as applicable and needed)
• Low potassium diet counseling
6.3.2.2. Visits T2 (Day 8±1), T4 (Day 22±1), T6 (Day 36±1), and T8 (Day 50±1)

The following activities will be performed:

- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
  - If the local lab serum K⁺ ≥ 6.2, repeat serum potassium test from a new blood draw
- IXRS entry of a local lab serum potassium value
- Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Losartan and/or spironolactone reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient retraining regarding ACR collection

6.3.2.3. Visits T3 (Day 15±1) and T7 (Day 43±1)

The urine ACR value for each of these visits will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will be performed:

- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
  - If the local lab serum K⁺ ≥ 6.2, repeat serum potassium test from a new blood draw
- Serum chemistry panel (central lab)
- Urine ACR (central lab): 3 different samples collected:
  - 2 days before the visit
  - 1 day before the visit
  - at the visit
- IXRS entry of a local lab serum potassium value
- Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Losartan and/or spironolactone reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment

6.3.2.4. Visit T5 (Day 29±1)

The urine ACR value for the T5 Visit will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will be performed:

- Body weight
- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
  - If the local lab serum K+ ≥ 6.2, repeat serum potassium test from a new blood draw
- Other laboratory tests (see Appendix A and B)
  - Serum chemistry panel (central lab)
  - Urinalysis (central lab)
  - Urine ACR (central lab): 3 different samples collected:
    - 2 days before the visit
6.3.2.5. Visit T9 (Day 57±1)

Day 57 is the intended last day of the RLY5016 Treatment Initiation Period.

At the T9 Visit (Day 57), patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule.

Titrations at the T9 Visit will be based on the Long-Term Maintenance Period titration algorithm.

The urine ACR value for this visit will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will occur:

- Physical examination
- Body weight
- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
  - If the local lab serum K⁺ ≥ 6.5, repeat serum potassium test from a new blood draw
- Other central laboratory tests (see Appendix A and B)
  - Serum chemistry panel
  - HbA1c measurement
  - Hematology (CBC)
  - Urinalysis
  - Urine ACR: 3 different samples collected:
    - 2 days before the visit
    - 1 day before the visit
    - at the visit
  - Serum pregnancy test (females of child-bearing potential only)
  - Serum fluoride
  - Blood and urine samples for potential biomarker analysis
- IXRS entry of a local lab serum potassium value
- Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed).
- Losartan and/or spironolactone accountability and patient retraining (as applicable and needed).
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient retraining regarding ACR collection (N/A if Weekly Maintenance Visits are required)

6.4. Long-Term Maintenance Period

RLY5016 doses may be adjusted during the Long-Term Maintenance Period according to the titration algorithm (see Section 3.6.2, Appendix E). Specific attention should be paid whenever the local lab serum K⁺ value during the Long-
Term Maintenance Period is either $< 3.5$ OR $\geq 6.5$ mEq/L (see Section 4.3).

On Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 the patient shall present for Visits M1, M2, M3, M4, M5, M6, M7, M8, M9 and M10 (respectively) as detailed further in this section.

If during the Long-Term Maintenance Period, a Mandatory Safety Visit or a Weekly Visit coincides with a Monthly Visit (M1-M11), all additional applicable monthly visit assessments must be performed according to the schedule of events.

6.4.1. **Study Visits M1 (Week 12 ±3 days), M4 (Week 24 ±3 days) and M7 (Week 36 ±3 days)**

The urine ACR value for the M1, M4 and M7 Visits will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will be performed:

- Body weight (except at Visit M1)
- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
  - If the local lab serum K$^+$ $\geq 6.5$, repeat serum potassium test from a new blood draw
- Other central laboratory tests (see Appendix A and B)
  - Serum chemistry panel
  - HbA1c measurement
  - Hematology (CBC)
  - Urinalysis
  - Urine ACR: 3 different samples collected:
    - 2 days before the visit
    - 1 day before the visit
6.4.2. Study Visits M2 (Week 16 ±3 days), M3 (Week 20 ±3 days), M5 (Week 28 ±3 days), M6 (Week 32 ±3 days), M8 (Week 40 ±3 days), M9 (Week 44 ±3 days) and M10 (Week 48 ±3 days)

The following activities will be performed:

- Resting heart rate and sitting blood pressure
- Serum potassium (local and central lab)
  - If the local lab serum $K^+ \geq 6.5$, repeat serum potassium test from a new blood draw
- Other central laboratory tests (see Appendix A and B)
  - Serum chemistry panel
- IXRS entry of a local lab serum potassium value
- Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Losartan and/or spironolactone accountability and patient retraining (as applicable and needed)
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient retraining regarding ACR collection (at M3, M6 and M10 Visits only)
6.5. **End of Treatment or Early Termination (M11/ET Week 52 ± 3days)**

Week 52 Visit is the intended last day of RLY5016 treatment. In case the patient withdraws or early terminates at any time prior to the M11 Visit (Week 52), the M11 Visit activities shall be performed.

The urine ACR value for the End of Treatment Visit (M11/ET) will represent an average ACR value obtained from samples collected at 3 different time points: two days before the visit, one day before the visit, and at the visit. Patients should be instructed to collect urine specimens from the second morning void.

The following activities will occur:

- Physical examination
- Body weight
- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
- Other central laboratory tests (see Appendix A and B)
  - Serum chemistry panel
  - HbA1c measurement
  - Hematology (CBC)
  - Urinalysis
  - Urine ACR: 3 different samples collected:
    - 2 days before the visit
    - 1 day before the visit
    - at the visit
  - Serum pregnancy test (females of child-bearing potential only)
  - Serum fluoride
  - Blood and urine samples for potential biomarker analysis
- IXRS entry of a local lab serum potassium value
- RLY5016 discontinuation, reconciliation and accountability
- Losartan and/or spironolactone, reconciliation, accountability, and
- Losartan and/or spironolactone discontinuation for patients with serum $K^+ > 5.0$ mEq/L
- Losartan and/or spironolactone dispensation and patient retraining for patients with serum $K^+ \leq 5.0$ mEq/L
- Low potassium diet counseling
- Adverse event assessment
- Concomitant medications assessment

6.6. Other Visits

6.6.1. Mandatory Safety Visit

The following activities will occur:

- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting (as applicable)
- Serum potassium (local and central lab)
- IXRS entry of a local lab serum potassium value
- Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Low potassium diet counseling (if needed)
- Adverse event assessment
- Concomitant medications assessment

6.6.2. Weekly Maintenance Visits (±1 day)

The following activities should occur:

- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting
- Serum potassium (local and central lab)
- Assessment of patient compliance to per-protocol treatment
- Low potassium diet counseling (if needed)
- IXRS entry of a local lab serum potassium value
- Potential RLY5016 dose titration, reconciliation, dispensation, accountability, and patient retraining (as applicable and needed)
- Losartan and/or spironolactone accountability and patient retraining (as
applicable and needed)

- Adverse event assessment
- Concomitant medications assessment
- Dispensation of urine ACR collection cups and patient retraining regarding ACR collection (only at visit just prior to M1)

6.6.3. Unscheduled Visit

For any Unscheduled Study Visit the following activities must occur:

- Resting heart rate and sitting blood pressure
- Serum potassium (local and central lab)
- Serum chemistry panel (central lab)
- Low potassium diet counseling
- Assessment of patient compliance to per-protocol treatment
- Adverse event assessment
- Concomitant medications assessment

The following activities are optional according to the Investigator’s discretion:

- ECG, 12-lead, resting
- And any other procedures deemed clinically necessary

6.7. Follow-up Period

6.7.1. F1 – F5 Visits

There are 2 different follow-up schedules which will depend on final local lab serum potassium level (see Section 3.7). Patients will either return for 2 visits (at 3±1 day and 7±3 days; F1 and F2, respectively) or for 5 visits (at 3±1 day, 7±3 days, 14±3 days, 21±3 days, and 28±3 days; F1, F2, F3, F4 and F5, respectively) after RLY5016 discontinuation.

The following activities will be performed at follow-up visits:

- Resting heart rate and sitting blood pressure
- ECG, 12-lead, resting at the last follow-up visit (or at the Investigator’s
discretion)

- Serum potassium (local and central lab)
- Serum chemistry panel (central lab) at visits F2 and F5 only
- IXRS entry of a local lab serum potassium value
- Losartan and/or spironolactone reconciliation, dispensation, accountability, discontinuation at F5 (if applicable)
- Adverse event assessment
- Concomitant medications assessment

6.7.2. **Survival Follow-up Telephone Contact**

For those patients who discontinue from the study, additional survival data will be collected after the last performed study visit and will consist of phone contacts conducted every 3 months starting from the last study visit until one year after the patient’s Baseline T0 Visit. The following information will be collected during each telephone contact: patient’s survival status and, if patient has deceased, date and cause of death if available. Survival status data will not be analyzed as part of the safety outcomes of the study. Any deaths reported during a survival follow-up telephone contact will be considered non-treatment emergent.

7. **ASSESSMENT OF EFFICACY AND SAFETY**

7.1. **Primary Variables**

7.1.1. **Treatment Initiation Period Primary Efficacy Variable**

The mean change in serum potassium from baseline (T0) to week 4 or prior to the initiation of RLY5016 dose titration (if occurs before week 4) will be considered as the primary efficacy variable.

7.1.2. **Long-Term Maintenance Period Primary Safety Variable**

The frequency and severity of adverse events during the Long-Term Maintenance Period of the trial will be the primary safety variable.
7.2. Efficacy Variables

7.2.1. Treatment Initiation Period Secondary Efficacy Variables

Efficacy shall also be assessed by the following measures:

- Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration
- Proportion of patients maintaining the starting RLY5016 dose at weeks 4 and 8
- Mean change in serum potassium from baseline (T0) to post-baseline visits
- Mean change in serum potassium from end of RLY5016 treatment to follow-up visits
- Proportion of patients requiring RLY5016 titration
- Proportion of patients achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by end of week 8
- Mean time to first serum K$^+$ in the range of 4.0 – 5.0 mEq/L
- Mean time to first RLY5016 titration
- Mean number of RLY5016 titrations
- Proportion of patients who maintain serum K$^+$ in the range of 3.5 – 5.5 mEq/L by visit and during the entire Treatment Initiation Period
- Proportion of patients who maintain serum K$^+$ in the range of 4.0 – 5.0 mEq/L by visit and during the entire Treatment Initiation Period
- Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria
- Mean change in blood pressure from R0 to weeks 4 and 8
- Mean change in urine albumin to creatinine ratio (ACR) from R0 to weeks 4 and 8
- Proportion of patients with ≥ 35% reduction in urine ACR from R0 to weeks 4 and 8
- Proportion of patients with urine ACR ≥ 500 mg/g at R0 who achieve ACR < 500 mg/g at weeks 4 and 8
- Proportion of patients with urine ACR ≥ 300 mg/g at R0 who achieve ACR < 300 mg/g at weeks 4 and 8
7.2.2. Long-Term Maintenance Period Efficacy Variables

- The interpolated time serum potassium concentrations stay within the target range of 3.8 to 5.0 mEq/L over the duration of the Long-Term Maintenance Period of the trial
- Proportion of patients with serum potassium values below, within, and above various ranges by visit
- Mean change in serum potassium from baseline (T0) to post-baseline visits
- Mean change in serum potassium from end of RLY5016 treatment to follow-up visits
- Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria
- RLY5016 doses by visit
- Number and type of RLY5016 titrations by visit
- Mean change in blood pressure from R0 visit to months 6 and 12
- Mean change in eGFR from R0 visit to months 6 and 12
- Mean change in urine albumin to creatinine ratio (ACR) from R0 visit to months 6 and 12
- Proportion of patients with ≥ 35% reduction in urine ACR from R0 visit at months 6 and 12
- Proportion of patients with urine ACR ≥ 500 mg/g at R0 visit who achieve ACR < 500 mg/g at months 6 and 12
- Proportion of patients with urine ACR ≥ 300 mg/g at R0 visit who achieve ACR < 300 mg/g at months 6 and 12

7.2.3. Exploratory Measures

Additional blood and urine will be collected at the First Run-In Visit (R0), Baseline T0 (Day 1), T5 (Day 29), T9 (Day 57), M4 (Week 24) and M11 (Week 52 or ET) and may be analyzed using non-genetic tests for one or more of the following: aldosterone and markers of aldosterone pharmacology, cardiac hormones, and renal injury biomarkers (e.g., BNP, galectin-3, NT-proBNP, MR-proANP, CRP, CT-proAVP, CT-proET-1, MR-proADM, cystatin C, ADMA, FGF23, PTH, adiponectin, apoA-IV, vitamin D (25-hydroxy-vitamin D; 1,25 dihydroxy-vitamin D), NGAL, KIM-1, podocyte, and ferritin).
7.3. Safety Parameters

Safety and tolerability will be assessed by the incidence and severity of adverse events, clinical laboratory measurements, serum fluoride, vital signs, and ECG parameters. Other safety outcome measures are:

- Proportion of patients who meet < 3.5 mEq/L serum potassium withdrawal criteria.
- Incidence of hypomagnesemia (serum magnesium < 1.8 mg/dL).
- Incidence of cardiovascular events and renal events
- Mean change in HbA1c from R0 to months 6 and 12

7.3.1. Adverse Events

Adverse events which are reported, observed, or elicited by indirect questioning will be collected from the time of signing the informed consent and throughout the study until the last study visit. Whenever possible, any related adverse event or serious adverse event that is ongoing at the last study visit will be followed until it resolves or becomes stable.

7.3.2. Blood Laboratory Safety Tests

All laboratory tests specified in the Schedule of Events (Appendix A) and in the Listing of Laboratory Assays (Appendix B) will be performed by central labs. In addition to central lab assessments, local labs will perform serum potassium measurements at all study visits.

Serum potassium (local and central lab) should be collected at approximately the same time in the morning for the same patient at ALL Study Visits (including Mandatory Safety Visit and any Unscheduled Visit). Serum potassium will be measured at every study visit and dosing decisions will be based on local lab results. To minimize the variance in serum potassium results, and avoid hemolysis of samples, specimen collection and handling must strictly follow specific instructions provided in the Laboratory Manual.
Serum chemistry

A central lab sample will be collected at the following visits: Screening (S1), Baseline T0 (Day 1), T3 (Day 15), T5 (Day 29), T7 (Day 43), T9 (Day 57), all Long-Term Maintenance Period Visits (M1 Week 12 - M11 Week 52/ET), F2 (7-Day Follow-up), F5 (28-Day Follow-up) and at any Unscheduled Visit. Serum magnesium will be measured as a part of the serum chemistry panel. Patients with a serum magnesium below 1.8 mg/dL at any time during the study should be treated per standard of care.

In addition to a central lab aliquot (full serum chemistry panel), another serum aliquot will be processed by local lab for ALT, AST, serum magnesium, and serum creatinine assays only at the Screening (S1) Visit for patients whose screening serum K$^+$ > 5.0 – < 6.0 mEq/L.

Hemoglobin A1c (HbA1c) (central lab) will be collected at Screening S1 Visit, T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36) and M11 (Week 52 or ET) Visits.

Hematology (CBC) (central lab) will be collected at Screening (S1), Baseline T0 (Day 1), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36) and M11 (Week 52 or ET) Visits.

Serum pregnancy test (central lab) will be performed at Screening (S1), Baseline T0 (Day 1), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36), and M11 (Week 52 or ET) for females of child-bearing potential only.

Serum fluoride (central lab) will be collected at Baseline T0 (Day 1), T5 (Day 29), T9 (Day 57), M4 (Week 24), and M11 (Week 52 or ET) Visits.

Detailed sample collection, handling, processing, and shipment instructions will be provided in the Laboratory Manual.
7.3.3. Urinalysis

The urinalysis (central lab) will be performed at Screening (S1), Baseline T0 (Day 1), T5 (Day 29), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36), and M11 (Week 52 or ET) Visits.

7.3.4. Urine Albumin and Creatinine, Urine Albumin-to-Creatinine Ratio (ACR)

The urine albumin and creatinine tests (central lab) and calculation of the corresponding urine ACR values (central lab) will be performed on urine collected at Screening (S1), each Run-In Visit (R0, R1, R2, and R3), Baseline T0 (Day 1), T3 (Day 15), T5 (Day 29), T7 (Day 43), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36) and M11 (Week 52 or ET) Visits. Sites will train patients to collect urine 1 and/or 2 days before scheduled study visits according to Section 6 and Appendix A (Schedule of Events).

7.3.5. Urine Pregnancy Test

All women of child-bearing potential must have negative urine pregnancy test on Baseline T0 (Day 1) before dispensation of RLY5016. This test will be performed by the local lab at the Baseline T0 (Day 1) Visit only.

7.3.6. Abnormal Laboratory Tests

The Investigator will monitor the laboratory test findings. If any laboratory test is abnormal during the course of the study, it will be followed at the discretion of the Investigator. Abnormal laboratory tests will be considered AEs if they are associated with symptoms or lead to a diagnosis, lead to discontinuation of RLY5016, require treatment or patient referral, or are clinically significant in their own right (see Section 8.1.1). In such cases, they must be reported on the Adverse Event Form.

7.3.7. Resting Heart Rate and Sitting Blood Pressure

Resting heart rate and sitting blood pressure will be assessed at all Study Visits including any Mandatory Safety Visit, any Weekly Maintenance Visit, and at any
Unscheduled Visit as detailed in Appendix A (Schedule of Events).

7.3.8. **Physical Examination**

A physical examination will be performed, whenever possible, by the same member of the study staff for this protocol, at Screening (S1), Baseline T0 (Day 1), T9 (Day 57), and M11 (Week 52 or ET) Visits. This will include the physical examination of the following body areas and systems: head and neck, abdomen, chest, cardiovascular, respiratory, musculoskeletal, skin, neurological, and endocrine.

Body weight will be measured at Screening (S1), Baseline T0 (Day 1), T5 (Day 29), and T9 (Day 57), M4 (Week 24), M7 (Week 36), and M11 (Week 52 or ET) Visits.

Body height will be measured at the Screening (S1) Visit only. The body mass index (BMI) will be calculated at Screening (S1), T9 (Day 57) and M11 (Week 52 or ET) Visits.

7.3.9. **Electrocardiogram (ECG)**

12-lead, resting ECGs will be recorded and assessed by a qualified individual at Screening (S1), the First Run-In Visit (R0), Baseline T0 (Day 1), all Study Visits in the Treatment Initiation Period, any Weekly Maintenance Visit, M1 (Week 12), M4 (Week 24), M7 (Week 36), M11 (Week 52 or ET), and last Follow-up Visit (F1-F5).

ECGs at a Mandatory Safety Visit or Unscheduled Visit may occur at the discretion of the Investigator. Machine reported ECG intervals and any abnormal ECG findings will be recorded.

7.3.10. **Estimated Glomerular Filtration Rate (eGFR)**

The estimated Glomerular Filtration Rate (eGFR) will be calculated by the central lab using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [45] at the following Study Visits: Screening (S1), Baseline T0 (Day 1), T3 (Day 15), T5 (Day 29), T7 (Day 43), T9 (Day 57), all monthly Study Visits in the Long-Term Maintenance Period (M1 – M11/ET), F2 (7-Day Follow-up), F5 (28-Day Follow-up) and at any Unscheduled Visit.
The Cohort 3 Screening (S1) local eGFR will be calculated by the local lab using the CKD-EPI [45] or MDRD equation [11]. If local lab does not calculate eGFR using either of these equations, Investigators should enter reported local lab serum creatinine value and patient’s age, gender, and race in the automatic eGFR calculator available at: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

8. ADVERSE EVENT COLLECTION AND REPORTING

8.1. Definitions

8.1.1. Definition of Adverse Event (AE)

An adverse event (AE) is defined as: “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment” (International Conference on Harmonisation [ICH] Guideline “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” E2A) [46]. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes: 1) any new medical condition, sign or symptom or newly diagnosed event that occurs during the AE reporting period (see Section 8.2.1), including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period; 2) a previous condition that has worsened in severity or frequency or changed in character during the AE reporting period; and 3) complications that occur as a result of protocol-mandated interventions.

For the purposes of this protocol, events that are not considered adverse events include:

- Endpoints, even if they worsen (e.g., hyperkalemia, proteinuria, etc.)
- Anticipated fluctuating signs or symptoms of a pre-existing medical condition (e.g., tremor in a patient with Parkinson’s Disease; migraine episodes) that
have not worsened in severity or frequency or changed in character during the AE reporting period

- Surgeries or medical procedures – the medical condition (new or worsened) that led to the surgery or medical procedure would be the reported adverse event (e.g., appendicitis resulting in appendectomy – appendicitis would be reported as the adverse event)

- Overdose without clinical signs or symptoms

- Beneficial changes (e.g., sleeping better; less irritable)

- Pregnancy (see Section 8.4)

Out of range laboratory results, ECGs, vital signs and other safety assessments will be considered AEs if they meet at least one of the following criteria:

- Associated with symptoms or lead to a diagnosis (in such case the symptom or diagnosis should be recorded as an AE)

- Lead to discontinuation of RLY5016

- Require treatment or patient referral for further testing outside the protocol (repeat testing or titration are within protocol procedures)

- The abnormality is deemed significant in its own right (e.g., asymptomatic creatinine kinase > 5000 International Units per liter)

8.1.2. **Definition of Serious Adverse Event (SAE)**

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death.

- Is life-threatening. (This refers to a patient who was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it had been more severe).

- Requires inpatient hospitalization or prolongation of existing hospitalization, with the exception of:
- Visits to the emergency room or hospital department that do not result in an overnight hospital admission
- Elective surgery for a pre-existing condition that has not worsened
- Routine health assessments requiring admission
- Social admission (lack of housing, family circumstances, etc.)
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered medically significant by the Investigator or requires intervention to prevent any one of the outcomes above (e.g. blood dyscrasias; convulsions).

8.2. Procedures for Eliciting, Recording and Reporting Adverse Events

8.2.1. Adverse Event Reporting Period

Adverse events, including Serious Adverse Events, will be collected throughout the study period, from the time the patient signs the informed consent form until up to 7 or 28 days after the last dose of RLY5016 (Follow-up Visit F2 or F5, respectively). Any related adverse event or SAE that is ongoing at the last study visit will be followed, whenever possible, until it resolves or becomes stable.

8.2.2. Eliciting Adverse Events

Information on AEs and SAEs will be elicited at each AE assessment time point specified in the Schedule of Events by asking the patient an open-ended question such as: "Since you were last asked, have you felt unwell or different from usual in any way?" Adverse events may also be reported spontaneously at any time.

8.2.3. Assessing Adverse Events

The following guidelines for rating severity of adverse events should be used:

**Mild:** Awareness of signs or symptoms, but easily tolerated; no disruption of normal activities; symptoms are transient and would not require medication or medical evaluation

**Moderate:** Discomfort enough to cause interference with usual activities and treatment may be required
Severe: Incapacitating with inability to do work or do usual activities; may require medical evaluation and/or treatment; the investigational product (RLY5016) may have been discontinued

The term “severe” is often used to describe the intensity of a specific event; the event itself, however, may be of relatively minor medical significance, such as severe headache. This is not the same as serious, which is a regulatory definition (see Section 8.1.2).

The relatedness of the AE to RLY5016 will be determined by the Investigator using the following definitions:

Not Related: The event is related to an etiology other than the study product (the alternative etiology must be documented in the study subject's medical record).

Related: There is a temporal association between the event and the administration of study product and a plausible mechanism for the event to be related to the study product, and causes other than the study product have been ruled out and/or the event reappeared on re-exposure to the study product.

8.2.4. Recording Adverse Events

All AEs and SAEs, whether spontaneously reported by the patient or elicited or noted by study staff, will be recorded in the patient’s medical record and on the appropriate AE case report form (CRF) or electronic CRF (eCRF) page. In addition, there must be a record of SAEs on the SAE Report Form.

- Adverse events should be recorded using the words of the patient to describe the adverse event (verbatim term), with two exceptions: If the verbatim is vague or ambiguous (e.g., cramps), the study staff should try to obtain clarification by asking a follow-up questions (e.g., what kind of cramps?) and record the words the patient used to clarify the event (e.g., menstrual cramps, calf muscle cramps)

- If the patient reports a group of symptoms and the investigator is comfortable with a unifying diagnosis, the diagnosis should be recorded (e.g.,
rhinopharyngitis instead of runny nose, cough, sore throat and sneezing). If a diagnosis is recorded, there is no need to record signs and symptoms separately.

The following information should be captured for each adverse event: date of onset and resolution, outcome, severity (as defined below), seriousness, relatedness to the investigational product, action taken with RLY5016 and treatments administered. Any treatment administered as a result of an AE should be recorded on the concomitant medication CRF.

8.3. Serious Adverse Events Reporting

8.3.1. SAE Notification

The Investigator has the obligation to report each SAE within 24 hours of knowledge of the occurrence. This includes events that occur within 7 days following completion of treatment with RLY5016. Additionally, if the Investigator learns of any serious adverse events that occurred after the follow-up period for which there is a reasonable possibility of relatedness to RLY5016, that event must be reported within 24 hours.

Serious adverse events must be reported by entering the SAE information into the SAE CRF in the Electronic Data Capture (EDC) system. If the event meets serious criteria and it is not possible to access the EDC, SAE reporting via a paper form will be required. The Investigator must complete a paper copy of SAE report form, scan, and fax/e-mail it to the contact provided in the Safety Plan.

The SAE information must be entered onto the SAE CRF as soon as the EDC system becomes accessible. All Serious Adverse Events should be followed until they are resolved or stabilized and all relevant information is compiled. Follow-up information must be handled in the same way and reported within the same time frame as the initial report.

Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. Death should be reported as an outcome and
not as an event.

The electronic or paper SAE Form will be completed with the following information at a minimum:

- Trial number/ trial center
- Name of reporter/investigator
- Patient identification number
- Adverse event term
- Date of onset
- Criteria of seriousness
- RLY5016 relatedness

Additional information must be provided when available, and any relevant records (hospital discharge, death certificate, etc.) must be attached.

8.3.2. SAE Expedited Reporting

Investigators will be notified of all SAEs requiring expedited reporting to regulatory authorities. The Investigator must review and file the safety report with the Investigator’s Brochure. Where required, the Investigator is responsible for assuring his/her respective IRB/IEC is notified.

8.4. Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female patient become pregnant or be suspected of being pregnant while participating in this study, the investigational product will be permanently discontinued, and the event must be reported to the sponsor upon receipt of information by the study staff. While the pregnancy is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Any pregnancy will be followed through delivery for the observation of any SAEs. Fatalities and spontaneous abortions must be reported as SAEs.
9. **STATISTICAL METHODS AND DATA ANALYSIS**

9.1. **Determination of Sample Size**

This is a multicenter, randomized, open-label, dose ranging study designed to determine the optimal starting dose for RLY5016 in patients with hypertension and diabetic nephropathy. This study will have approximately 300 patients randomized (50 patients per dose group) to ensure at least 252 patients (42 patients per dose group) will receive investigational product and provide primary efficacy data for data analysis assuming a 15% non-evaluable rate.

9.1.1. **Stratum 1**

Stratum 1 will have approximately 150 patients with baseline local lab serum K⁺ value > 5.0 – 5.5 mEq/L randomized in a 1:1:1 allocation ratio (50 patients per dose group) within each study cohort to ensure at least 126 patients (42 patients per dose group) will receive investigational product and provide primary efficacy data for data analysis assuming a 15% non-evaluable rate. A sample size of 42 patients for each RLY5016 dose group is based on an effect size of 0.5 for the primary efficacy measurement, change in serum K⁺ from baseline to Week 4 or prior to the initiation of RLY5016 dose titration. This sample size will have 90% power to detect statistically significant change at significant level of 0.05 within each dose group. This calculation is based on a two-sided one sample paired t-test, and a significance level of $\alpha = 0.05$. Assuming a 15% non-evaluable rate, approximately 150 patients are expected to be randomized in this Stratum 1.

9.1.2. **Stratum 2**

Stratum 2 will have approximately 150 patients with baseline local lab serum K⁺ value > 5.5 – < 6.0 mEq/L randomized in a 1:1:1 allocation ratio (42 patients per dose group) within each study cohort to ensure at least 126 patients (42 patients per dose group) will receive investigational product and provide primary efficacy data for data analysis assuming a 15% non-evaluable rate. A sample size of 42 patients for each RLY5016 dose group is based on an effect size of 0.5 for the primary efficacy measurement, change in serum K⁺ from baseline to Week 4 or prior to the initiation
of RLY5016 dose titration. This sample size will have 90% power to detect statistically significant change at significant level of 0.05 within each dose group. This calculation is based on a two-sided one sample paired t-test, and a significance level of $\alpha = 0.05$. Assuming a 15% non-evaluable rate, approximately 150 patients are expected to be randomized in this Stratum 2.

9.2. Tests of Hypothesis and Significance Levels

The primary null hypothesis to be tested in this study is that the least squares estimate of the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration within each RLY5016 dose group equals zero.

The statistical tests used for the analysis of baseline variables and efficacy parameters will be performed at the $\alpha = 0.05$ significance level. All tests are two-sided.

9.3. Randomization and Blinding of the Treatment Assignment

This is a multicenter, randomized, open-label, dose ranging study. At the Initial Run-In Visit (R0) eligible patients without hyperkalemia who are taking at least one ACEI or ARB drug will discontinue all ACEI or ARB drugs and start losartan 100 mg/d (Cohort 1). Eligible patients who present with hyperkalemia at either S1 or R0 Visit and who are taking at least one ACEI or ARB drug will continue on their current dose of ACEI and/or ARB drug (Cohort 3).

However based on Cohort 1 and/or 3 enrollment data, Cohort 2 may be re-activated. Cohort 2 patients will remain on their current dose of ACEI and/or ARB drug and add spironolactone 25 mg/d.

At the Randomization Visit (T0), patients will be assigned to each of two randomization strata based on the baseline local lab serum potassium level:

- Stratum 1: serum K+ value $> 5.0 – 5.5$ mEq/L
- Stratum 2: serum K+ value $> 5.5 – < 6.0$ mEq/L
Patients in Stratum 1 will be randomized in a 1:1:1 allocation ratio to receive one of three RLY5016 starting doses: 10 g/d, 20 g/d, or 30 g/d within each study cohort. Patients in Stratum 2 will be randomized in a 1:1:1 allocation ratio to receive one of three RLY5016 starting doses: 20 g/d, 30 g/d, or 40 g/d within each study cohort.

9.4. Baseline Comparability

Demographics and baseline characteristics will be summarized by dose group for all randomized patients. Data will be pooled for all study centers for baseline data analysis.

9.4.1. Analysis of Stratum 1 Baseline Data

The F test of the Type III treatment factor from a one-way analysis of variance (ANOVA) model including only the treatment factor will be used to analyze the numeric variables. The Fisher's exact test will be used to analyze the categorical data.

9.4.2. Analysis of Stratum 2 Baseline Data

The F test of the Type III treatment factor from a one-way analysis of variance (ANOVA) model including only the treatment factor will be used to analyze the numeric variables. The Fisher's exact test will be used to analyze the categorical data.

9.5. Analysis of Efficacy Data

For the analysis of serum potassium data, the central lab serum potassium values will be used for the efficacy data analyses. Certain analyses may be repeated using local lab serum potassium values. Efficacy data obtained more than one day after the discontinuation of the last dose of investigational product will not be used for the efficacy data analysis.

Sections related to the analysis of efficacy data are specified by topic in section 9.5.1.
9.5.1. **Efficacy Parameters**

The primary efficacy parameter is the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration (if occurs before week 4).

The secondary efficacy parameters for the Treatment Initiation Period are:

1. Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration
2. Proportion of patients maintaining the starting RLY5016 dose at weeks 4 and 8
3. Mean change in serum potassium from baseline (T0) to post-baseline visits
4. Mean change in serum potassium from end of RLY5016 treatment to follow-up visits
5. Proportion of patients requiring RLY5016 titration
6. Proportion of patients achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by end of week 8
7. Mean time to first serum K⁺ in the range of 4.0 – 5.0 mEq/L
8. Mean time to first RLY5016 titration
9. Mean number of RLY5016 titrations
10. Proportion of patients who maintain serum K⁺ in the range of 3.5 – 5.5 mEq/L by visit and during the entire Treatment Initiation Period
11. Proportion of patients who maintain serum K⁺ in the range of 4.0 – 5.0 mEq/L by visit and during the entire Treatment Initiation Period
12. Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria
13. Mean change in blood pressure from R0 to weeks 4 and 8
14. Mean change in urine albumin to creatinine ratio (ACR) from R0 to weeks 4 and 8
15. Proportion of patients with ≥ 35% reduction in urine ACR from R0 to weeks 4 and 8
16. Proportion of patients with urine ACR ≥ 500 mg/g at R0 who achieve ACR < 500 mg/g at weeks 4 and 8
17. Proportion of patients with urine ACR ≥ 300 mg/g at R0 who achieve ACR < 300 mg/g at weeks 4 and 8
18. Change in blood and urine biomarkers from R0 to T0, weeks 4 and 8
The efficacy parameters for the Long-Term Maintenance Period are:

(1) The interpolated time serum potassium concentrations stay within the target range of 3.8 to 5.0 mEq/L over the duration of the Long-Term Maintenance Period of the trial

(2) Proportion of patients with serum potassium values below, within, and above various ranges by visit

(3) Mean change in serum potassium from baseline (T0) to post-baseline visits

(4) Mean change in serum potassium from end of RLY5016 treatment to follow-up visits

(5) Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria

(6) RLY5016 doses by visit

(7) Number and type of RLY5016 titrations by visit

(8) Mean change in blood pressure from R0 visit to months 6 and 12

(9) Mean change in eGFR from R0 visit to months 6 and 12

(10) Mean change in urine albumin to creatinine ratio (ACR) from R0 visit to months 6 and 12

(11) Proportion of patients with ≥ 35% reduction in urine ACR from R0 visit at months 6 and 12

(12) Proportion of patients with urine ACR ≥ 500 mg/g at R0 visit who achieve ACR < 500 mg/g at months 6 and 12

(13) Proportion of patients with urine ACR ≥ 300 mg/g at R0 visit who achieve ACR < 300 mg/g at months 6 and 12

(14) Change in blood and urine biomarkers from R0 to months 6 and 12

9.5.2. Analysis Population and Pooling of Investigators

The main analysis of the primary efficacy parameter and secondary efficacy parameters will include intent-to-treat (ITT) population. The ITT population includes all randomized patients who received investigational product. Efficacy data collected from all study centers will be pooled for data analysis.

9.5.3. Definition of Baseline and Endpoint Measurements

The baseline measurement is the last available measurement taken prior to the start of investigational product administration. The primary efficacy endpoint is the central
lab serum potassium data obtained at week 4 or prior to the initiation of RLY5016 dose titration. For those patients who required RLY5016 dose titration before week 4, the endpoint is the last observed data prior to the first titration. For patients who prematurely discontinued investigational product without RLY5016 dose titration and prior to week 4, the endpoint is the last observed data prior to termination.

9.5.4. Methods for the Analysis of Stratum 1 Efficacy Data:

A parallel lines analysis of covariance (ANCOVA) model will be used for the analysis of the primary efficacy measurement. This ANCOVA model will include the treatment factor and baseline serum potassium as the covariate. The least squares estimate of the mean change of each treatment and its 95% confidence interval (CI) will be presented. A 95% CI of the pairwise difference between any two RLY5016 dose groups in the mean change of serum potassium will be constructed.

An ANOVA model or ANCOVA model will be used for the analysis of continuous secondary efficacy measurements. The ANOVA model will include the treatment factor. The parallel lines ANCOVA model will include the treatment factor, and baseline measurement as the covariate.

In addition, Mixed-Effect Model Repeated Measure (MMRM) model will be used to analyze natural log-transformed ACR data.

Patients from all study centers will be pooled for the analysis of the categorical outcome data. For the analysis of the dichotomous outcome data, a two-sided Fisher’s exact test will be used for the overall comparison among all dose groups. In addition, a two-sample Z test on two proportions between two RLY5016 dose groups will be performed. The difference between two proportions and its 95% CI will be presented.

9.5.5. Methods for the Analysis of Stratum 2 Efficacy Data:

A parallel lines analysis of covariance (ANCOVA) model will be used for the analysis of the primary efficacy measurement. This ANCOVA model will include the
treatment factor and baseline serum potassium as the covariate. The least squares estimate of the mean change of each treatment and its 95% confidence interval (CI) will be presented. A 95% CI of the pairwise difference between any two RLY5016 dose groups in the mean change of serum potassium will be constructed.

An ANOVA model or ANCOVA model will be used for the analysis of continuous secondary efficacy measurements. The ANOVA model will include the treatment factor. The parallel lines ANCOVA model will include the treatment factor, and baseline measurement as the covariate.

In addition, Mixed-Effect Model Repeated Measure (MMRM) model will be used to analyze natural log-transformed ACR data.

Patients from all study centers will be pooled for the analysis of the categorical outcome data. For the analysis of the dichotomous outcome data, a two-sided Fisher’s exact test will be used for the overall comparison among all dose groups. In addition, a two-sample Z test on two proportions between two RLY5016 dose groups will be performed. The difference between two proportions and its 95% CI will be presented.

9.5.6. Methods for the Analysis of Efficacy Data Collected for the Long-Term Maintenance Period:

Data collected for the Long-Term Maintenance Period will be summarized descriptively. Patients from all study centers will be pooled for the analysis of the numeric and categorical outcome data.

9.6. Interim Data Analysis

An interim data analysis will be performed for this study based on study data collected from approximately 120 patients (20 patients per group) who completed week 4 treatment visit or prematurely terminated study and had primary efficacy data. The mean change in central lab serum potassium from baseline to week 4 (or prior to the initiation of RLY5016 dose titration) and its standard deviation for each
treatment group will be calculated based on this interim data set. These interim results may be used to determine the optimal starting RLY5016 dose for each stratum for future studies.

The optimal starting dose for each stratum will be determined based on key parameters including the following:

(1) Mean change in serum potassium during first 4 weeks of treatment
(2) Proportion of patients with serum K⁺ > 5.5 OR < 3.5 mEq/L at any time during the Treatment Initiation Period
(3) Time to first RLY5016 titration and type of RLY5016 titration
(4) Number of titrations needed to maintain serum K⁺ in the range of 4.0 – 5.0 mEq/L

Adverse events, serious adverse events and adverse events leading to early termination

9.7. Analysis of Safety Data

Safety variables consist of adverse events, cardiovascular events, renal events, clinical laboratory test results, vital signs, clinically significant ECG findings, newly observed physical examination abnormalities, and termination data. All randomized patients who received at least one dose of RLY5016 will be included in the analysis and summaries of safety data. An AE thesaurus, the Medical Dictionary for Regulatory Activities, (MedDRA) will be used to map each AE verbatim term to lowest level term, preferred term, and System Organ Class for summary purposes. Adverse events occurring while patients are on investigational product during the entire treatment period will be summarized by treatment group. All incidences of AEs will also be summarized. Other safety data, such as premature terminations, cardiovascular events, renal events, laboratory data, vital signs, ECG, and concomitant medications will be tabulated.

Since both the Treatment Initiation and Long-Term Maintenance Periods do not have a placebo control arm, mortality rates reported in the study will be compared using cohort matching with historical mortality rates reported in the United States
Renal Data System (USRDS) annual reports [47]. It is estimated that mortality rates reported in this study will range from 11% to approximately 25% depending on factors such as the age of the patients, the stage of chronic kidney disease and the presence of diabetes, hypertension and heart failure.

10. REGULATORY AND PROCEDURAL REQUIREMENTS

10.1. Ethical Considerations

The trial will be conducted in accordance with US FDA regulations, the ICH E6 guidelines for GCP, the Declaration of Helsinki, and IRB or independent ethics committee (IEC) requirements. The study will also be conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (EUCTD) for sites in the EU and all other applicable local and national laws and regulations governing the conduct of human clinical trials.

10.2. Institutional Review Board/Independent Ethics Committee

All Investigators participating in this study must be governed under an appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC). This protocol, the informed consent form, the Investigator’s Brochure and any information to be given to the subject must be reviewed and approved by the applicable IRB or IEC before a site can begin conducting any study-related activities. A copy of the IRB/IEC approval letter for the protocol and the informed consent document must be sent to Relypsa, or designee, prior to RLY5016 shipment. Any subject recruitment materials must also be approved by the IRB/IEC before the material is used for subject recruitment.

Subsequently, the Investigator is responsible for obtaining re-approval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the Investigator’s annual report and other required reports to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to Relypsa. The Investigator must also inform the IRB/IEC of any protocol changes or amendments, changes to the Investigator’s Brochure, expedited reports of SAEs submitted to regulatory...
authorities, and other significant safety concerns according to the IRB/IEC policy. Written documentation of IRB approval of protocol amendments must be received before the amendment is implemented. After completion or termination of the study, the Investigator will notify their IRB/IEC. The Investigator will comply with all IRB/IEC policies throughout the duration of the study.

10.3. Informed Consent

In compliance with GCP guidelines, all patients will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to the patient’s future medical care at the center. Each patient must agree to cooperate in all aspects of the study and must give informed written acknowledgment (signed informed consent document) to the Investigator prior to participation in the study. If the informed consent form (ICF) is revised during the study, active patients must sign the new version in order to continue participating in the study. For any updated or revised ICF, the subject record should state that written informed consent was obtained for the updated/revised consent form for continued participation in the trial. The ICF should be revised whenever there are changes to procedures in the amended protocol associated with procedures in the ICF or when new information becomes available that may affect the willingness of the subject to participate. Every patient will be given a copy of each version of the form that he/she signs before and during the study. In the United States, each ICF may also include authorization allowing the institution, Investigator and Relypsa to use and disclose personal health information in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

No patient is to participate in study activities until informed consent has been obtained. Documentation of the informed consent process and patient information discussion must appear in the patient’s medical record, and include a statement that informed consent was obtained prior to participation in the study. Signed acknowledgments (informed consent documents) must remain in the patients’ files and be available for verification by monitors, auditors, and/or regulatory agency
inspectors at any time. The final IRB/IEC-approved ICF must be provided to Relypsa for regulatory purposes.

10.4. Data Collection, Verification, and Quality Assurance and Control

10.4.1. Source Documentation

Source documents are original documents, data, and records (e.g., case histories, progress notes of the physician, nurses' notes, medical records, hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and records kept at the pharmacy or laboratories). Source data are contained in source documents and must be adequate to reconstruct all data transcribed onto the eCRFs and to evaluate the trial. Examples of source data include clinical findings, observations, enrollment summary information and ICF procedures, assessment of clinical significance for laboratory results, AE severity and seriousness, and Investigator’s opinion of AE relatedness to RLY5016.

The Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation for all patients.

Source documentation should be available at monitoring visits to verify entries made on Case Report Forms, as needed. Source documentation should also be available for verification by auditors and/or inspectors, as needed.

10.4.2. Electronic Case Report Forms (eCRFs)

An electronic Case Report Form (eCRF) is designed to record all of the protocol-required information to be reported to the sponsor on each trial patient. It is the Investigator’s responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on patients’ eCRFs. Data reported on the eCRF, which are derived from source documents, should be consistent with the source
documents or the discrepancies should be explained. An explanation should be given for all missing data.

All eCRF data and query resolutions must be completed only by the clinical trial personnel designated by the Investigator. All site staff will have proper training prior to accessing the electronic data capture (EDC) system.

Any change or correction to an eCRF will be tracked via an audit trail within the EDC system. The audit trail will contain the original data value, new data value, date changed, the user who made the change, and the reason(s) for the change.

CRFs should be completed in a timely manner to support the study timeline (i.e., do not wait for a monitoring visit before entering data into the eCRF).

10.4.3. Data Collection

Data from the eCRFs and queries will be tracked and entered into a 21 CFR Part 11 compliant, clinical database. The database system will be a secured, password-protected system with full audit trail utility.

Subject data will be reviewed via programmed quality checks and manually via data listings review by Relypsa and its designee. Data that appear inconsistent, incomplete, or inaccurate will be queried for site clarification. Data corrections will be updated to the database and tracked in the audit trail. Adverse events and concomitant medications will be coded using industry standard dictionaries [e.g., Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug dictionary].

10.4.4. Data Verification

The Investigator is responsible for reviewing, verifying, and approving all subject data (i.e., eCRFs and resolved queries).
10.4.5. **Data Quality Assurance**

The following steps will be taken to ensure that the trial is conducted by the investigational site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine site monitoring
- Documented protocol and GCP training
- eCRF and query review against source documents
- Collection of local laboratory normal ranges (if applicable)

10.4.6. **Data Quality Control**

The integrity and quality of subject data will be ensured by providing training and process instructions for the completion of the eCRFs, performing quality control checks, conducting ongoing clinical data review (including medical and safety reviews), and performing source data verification and data reconciliation.

10.5. **Monitoring and Inspections**

Site monitoring visits will be conducted by the sponsor or designee at regular intervals in accordance with FDA and ICH guidelines. The Investigator will permit sponsor or designee monitors to review and inspect facilities, and all records relevant to this study including source documents.

The Investigator will also permit sponsor or designee auditors, the IRB/IEC, FDA or other regulatory agency inspectors to review and inspect facilities, procedures, and all records relevant to this study. These records include but are not limited to: patient signed informed consent forms, source documentation, regulatory and essential documents, CRFs, and drug accountability records. If the FDA or other regulatory agency should schedule an inspection, the Medical Monitor should be notified immediately.
10.6. Protocol Deviations
The Investigator will not deviate from the protocol without prior written approval from the Medical Monitor, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. Any other change to the protocol must be implemented as an amendment to the protocol and must be approved by the IRB/IEC and Relypsa prior to implementation.

The governing IRB/IEC will be informed of all protocol changes by the Investigator in accordance with the IRB/IEC’s established procedure, and no deviations from the protocol of any type will be permitted without complying with the established IRB/IEC procedures.

10.7. Patient Recruitment
If an Investigator chooses to advertise for patients, whether in professional or consumer publications, radio, television, or the internet/website, all advertising must be approved by Relypsa and the IRB/IEC prior to initiation.

11. DATA HANDLING AND RECORDKEEPING
11.1. Patient Confidentiality
Individual patient’s medical information obtained as a result of this study is considered confidential and disclosure to unauthorized parties is prohibited. Patient confidentiality will be protected to the extent possible by utilizing patient identification code numbers and/or initials, instead of names. If results of this study are reported in medical journals or at meetings, the patient’s identity will not be disclosed.

Subject medical information obtained by this trial may only be disclosed to third parties as permitted by the ICF (if applicable, a separate authorization form to use and disclose personal health information signed by the subject, or unless permitted or required by law). With the patient’s written authorization, medical information may be provided to the patient’s personal physician or to other appropriate medical personnel responsible for the patient’s welfare.
11.2. Recordkeeping and Retention

The Investigator must maintain adequate records for the study, including protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572, local laboratory normal ranges (if applicable), protocol deviations, completed case report forms, queries, medical records, laboratory reports, signed informed consent documents, drug accountability/disposition records, adverse experience reports, information regarding patients who discontinued, all correspondence with the IRB/IEC and the sponsor, and other pertinent data.

All records are to be retained by the Investigator for a period of 2 years following the date when a marketing application for RLY5016 is approved. If no application is to be filed or if the application is not approved, the Investigator shall retain these records until 2 years after the study is completed and the FDA is notified. The Investigator will notify Relypsa in writing of the relocation of any study records away from the research facility after study closure. The Investigator must contact Relypsa in writing prior to the destruction of any study records, or in the event of loss of any study records.

11.3. Financing and Insurance

Financing and insurance are covered in the Clinical Trial Agreement and Clinical Trial Insurance Policy.

11.4. Publication Policy

A description of Relypsa’s publication terms is provided in the Clinical Trial Agreement.
12. REFERENCES


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http://www.fda.gov/ohrms/dockets/ac/02/briefing/3849b1_01_Merck.pdf. Table 20, Page 74.

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http://www.fda.gov/ohrms/dockets/ac/02/briefing/3829b1_01_Bristol-Myers.pdf. Page 92, Table 5.7.9.1A.

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47. United States Renal Data System (2011)
# APPENDIX A
## SCHEDULE OF EVENTS

<table>
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<tr>
<th>Study activity</th>
<th>Study Period</th>
<th>Screening</th>
<th>Run-In</th>
<th>Base-Line</th>
<th>TREATMENT INITIATION PERIOD</th>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE Assessment</td>
<td>X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Con Med Assessment</td>
<td>X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine ACR Supplies Dispensing</td>
<td>X X X X X X</td>
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</table>

<table>
<thead>
<tr>
<th>Mandatory Safety Visit</th>
<th>Unscheduled Visit</th>
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<tbody>
<tr>
<td>(X)</td>
<td>(X)</td>
</tr>
<tr>
<td>L&amp;C L&amp;C</td>
<td>L&amp;C L&amp;C</td>
</tr>
</tbody>
</table>
Abbreviations and Footnotes for Screening, Run-In and Treatment Initiation Periods Schedule of Events

C = Central lab testing; L&C = Both Local and Central lab testing (samples should be collected at approximately the same time in the morning for the same patient at all Study Visits including Mandatory Safety Visit and Unscheduled Visit); (X) = To be done if applicable

a. If the local lab serum K+ is > 5.0 - < 6.0 mEq/L at the Screening (S1) Visit (confirmed by repeat blood draw), perform a local lab ALT, AST, serum magnesium, and serum creatinine to evaluate Cohort 3 eligibility.
b. RLY5016 randomization assignment for Cohort 3 patients is based on all applicable eligibility criteria, when either the S1 or R0 Visit converts to the T0 Visit.
c. RLY5016 randomization assignment for Cohort 1 or 2 patients is based on all applicable eligibility criteria when one of the Run-In Visits (R1, R2 or R3) converts to the T0 Visit.
d. Perform a spot urine ACR for all patients at S1 only. Collect urine ACR samples for R0 at two different time points: one day before the visit, and at the visit. For all other visits, collect samples at three different time points: two days before the visit, one day before the visit, and at the visit. Cohort 3 patients may have 2 or 3 urine ACR samples depending on which visit was converted to T0.
e. Perform one unscheduled visit within 3 to 7 days for patients who are screen failures or enrollment failures after the initiation of losartan and/or spironolactone treatment during the Run-In Period.
f. Urine pregnancy test at the T0 Visit only will be performed by local laboratory.
g. Randomization to RLY5016 Starting Dose (serum K+ Stratum 1 or 2)
h. As applicable
i. Mandatory Safety Visit required the next day if the local lab serum K+ is 5.8 - < 6.2 mEq/L OR < 3.5 mEq/L at T1
j. Mandatory Safety Visit required in 1-3 days (see section 3.5.2.2)
k. Starting at the T9 Visit, patients will be titrated as needed according to the Long-Term Maintenance titration algorithm. Weekly Maintenance Visits may be required (see Long-Term Maintenance Schedule of Events [SOE]). Patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule.
l. The maximum allowed window for R0 Visit (calculated from the date of S1 Visit)
m. The maximum allowed window for T0 Visit (calculated from the date of previous study visit: S1, R0, R1, R2, or R3)

>>Remainder of Page Intentionally Left Blank<<
<table>
<thead>
<tr>
<th>Study activity</th>
<th>Study Period</th>
<th>LONG-TERM MAINTENANCE</th>
<th>Follow-up</th>
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</thead>
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<tr>
<td>Visit</td>
<td>M1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>M2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>M3&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Week</td>
<td>12</td>
<td>16</td>
<td>20</td>
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<tr>
<td>Window</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
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<td>Physical Examination</td>
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<td>Body Weight</td>
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<td>Heart Rate and Blood Pressure</td>
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<td>X</td>
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<tr>
<td>12-lead ECG</td>
<td>X</td>
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</tr>
<tr>
<td>Serum Chemistry</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Hematology (CBC)</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine ACR</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Pregnancy Test</td>
<td>C</td>
<td></td>
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</tr>
<tr>
<td>Serum Fluoride</td>
<td>C</td>
<td></td>
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<tr>
<td>Biomarker Analysis</td>
<td>C</td>
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<td>IXRS Entry</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>RLY5016 Dispensing and Titration&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Losartan / Spironolactone Dispensing</td>
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<td>Drug Accountability</td>
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<td>Low Potassium Diet Counseling</td>
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</tr>
<tr>
<td>AE Assessment</td>
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</tr>
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<td>Con Med Assessment</td>
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<td>X</td>
</tr>
<tr>
<td>Urine ACR Supplies Dispensing</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23-March-2012 126 CONFIDENTIAL
Abbreviations and Footnotes for Long-Term Maintenance, End of Treatment / Early Termination and Follow-up Periods

Schedule of Events

C = Central lab testing; L&C = Both Local and Central lab testing (samples should be collected at approximately the same time in the morning for the same patient at all Study Visits including Mandatory Safety Visit, Weekly Maintenance Visit and Unscheduled Visit); (X) = To be done if applicable

A. At the T9 Visit (see Treatment Initiation SOE), patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule.

B. Starting at Visit T9 and until Week 51 Visit, Mandatory Safety Visits may be required 1-3 and 7 days after the weekly/monthly maintenance visit (see section 3.6.2)

C. As applicable

D. If local lab serum K+ is ≤ 5.0 mEq/L at M11/ET, discontinue RLY5016 but continue all RAAS inhibitors and return for F1, F2, F3, F4 and F5 visits. If local lab serum K+ is > 5.0 mEq/L at M11/ET, discontinue RLY5016 and discontinue all RAAS inhibitors and return for F1 and F2 visits.

E. Mandatory 12-lead, resting ECG if this is the last Follow-up Visit.

F. Patients who discontinue from the study will be contacted every 3 months starting from the last study visit until one year after the patient’s Baseline T0 Visit.

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## APPENDIX B
### LISTING OF LABORATORY ASSAYS

<table>
<thead>
<tr>
<th>Serum Chemistry Panel:</th>
<th>Hematology (CBC):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>White blood cell count (WBC)</td>
</tr>
<tr>
<td>Albumin</td>
<td>Red blood cell count (RBC)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
<td>Hematocrit (Packed Cell Volume)</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>Mean cell volume (MCV)</td>
</tr>
<tr>
<td>Blood Urea Nitrogen (BUN)</td>
<td>Mean cell hemoglobin (MCH)</td>
</tr>
<tr>
<td>Calcium</td>
<td>Mean cell hemoglobin concentration (MCHC)</td>
</tr>
<tr>
<td>Creatine kinase (CK)</td>
<td>Platelet count</td>
</tr>
<tr>
<td>CK-MB (if CK is elevated)</td>
<td>Differential WBC</td>
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<tr>
<td>Creatinine (with eGFR)</td>
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</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td><strong>Serum Potassium (Primary Endpoint)</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Serum Potassium (Primary Endpoint)</td>
<td></td>
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<tr>
<td>Sodium</td>
<td></td>
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<tr>
<td>Total cholesterol</td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
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<td>Specific gravity</td>
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</tr>
<tr>
<td>Protein</td>
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</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
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</tr>
<tr>
<td>Leucocytes</td>
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<td>Nitrites</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c (HbA1c)</td>
<td></td>
</tr>
<tr>
<td>Urine Albumin and Creatinine (with ACR)</td>
<td></td>
</tr>
<tr>
<td>Serum Fluoride</td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test (females of child-bearing potential)</td>
<td></td>
</tr>
<tr>
<td>Blood and urine samples for potential non-genetic analysis of one or more</td>
<td></td>
</tr>
<tr>
<td>of the following: aldosterone and markers of aldosterone pharmacology,</td>
<td></td>
</tr>
<tr>
<td>cardiac hormones, and renal injury biomarkers (e.g., BNP, galectin-3, NT-</td>
<td></td>
</tr>
<tr>
<td>proBNP, MR-proANP, CRP, CT-proAVP, CT-proET-1, MR-proADM, cystatin C,</td>
<td></td>
</tr>
<tr>
<td>ADMA, FGF23, PTH, adiponecin, apoA-IV, vitamin D [25-hydroxy-vitamin D,</td>
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</tr>
<tr>
<td>1,25 dihydroxy-vitamin D], NGAL, KIM-1, podocyte, and ferritin)</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
</tbody>
</table>

**23-March-2012 128 CONFIDENTIAL**
APPENDIX C
RLY5016 TREATMENT INITIATION TITRATION FLOWCHART
VISITS T0 – T1

RLY5016 Treatment Initiation titration instructions will be provided by IXRS upon entry of the local lab serum potassium value.

Randomization Visit T0 (Day 1):
Randomization and Initiation of RLY5016 Treatment

Visit T1 (Day 3):
Local Lab Serum K⁺ Value (mEq/L):

<table>
<thead>
<tr>
<th>&lt; 3.5</th>
<th>3.5 – &lt; 5.8</th>
<th>5.8 – &lt; 6.2</th>
<th>≥ 6.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLY5016 Dose ↓ to 10 g/d or to 0 g/d¹</td>
<td>RLY5016 Dose ↑ to 60 g/d</td>
<td>Same Day Repeat Serum K⁺</td>
<td></td>
</tr>
<tr>
<td>Next Day Mandatory Safety Visit Local Lab Serum K⁺:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.5</td>
<td>3.5 – &lt; 4.0</td>
<td>≥ 4.0</td>
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</tr>
<tr>
<td>Is Current RLY5016 Dose 0 g/d?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLY5016 Dose Unchanged</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET Visit (Appendix F)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Next Day Mandatory Safety Visit
Did Serum K⁺ ↓ ≥ 0.4?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLY5016 Dose ↓ to 0 g/d</td>
<td></td>
</tr>
<tr>
<td>Visit T2 (Day 8) (Appendix D)</td>
<td></td>
</tr>
<tr>
<td>ET Visit (Appendix F)</td>
<td></td>
</tr>
</tbody>
</table>

¹ Decrease RLY5016 dose to 0 g/d only if the patient is currently on 10 g/d
APPENDIX D
RLY5016 TREATMENT INITIATION TITRATION FLOWCHART
(VISITS T2 – T8)

RLY5016 Treatment Initiation titration instructions will be provided by IXRS upon entry of the local lab serum potassium value.

<table>
<thead>
<tr>
<th>Visits: T2 (Day 8), T3 (Day 15), T4 (Day 22), T5 (Day 29), T6 (Day 36), T7 (Day 43), and T8 (Day 50):</th>
<th>Local Lab Serum K⁺ Value (mEq/L):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3.5 ¹</td>
</tr>
<tr>
<td><strong>Is Current RLY5016 Dose 0 g/d?</strong></td>
<td><strong>Same Day Repeat Serum K⁺</strong></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Did Serum K⁺ ↓ ≥ 0.4?²</strong></td>
<td><strong>Mandatory Safety Visit (1, 2, or 3 Days Later)</strong></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>RLY5016 Dose Unchanged</strong></td>
<td><strong>RLY5016 Dose ↓ by 10 g/d</strong></td>
</tr>
<tr>
<td><strong>ET Visit (Appendix F)</strong></td>
<td><strong>ET Visit (Appendix F)</strong></td>
</tr>
</tbody>
</table>

¹ If serum K⁺ remains < 3.5 mEq/L for 2 consecutive scheduled visits (one week apart) regardless of RLY5016 dose, patient must be withdrawn from the study
² Compared to the serum potassium value at the previous scheduled visit 1 week ago
³ Decrease RLY5016 dose to 0 g/d only if the patient is currently on 10 g/d
APPENDIX E
RLY5016 LONG-TERM MAINTENANCE TITRATION FLOWCHART
(VISITS T9 – WEEK 51)

RLY5016 Long-term Maintenance titration instructions will be provided by IXRS upon entry of the local lab serum potassium value. **Part 1:**

<table>
<thead>
<tr>
<th>Weekly or Monthly Visits: T9 (Day 57) through Week 51</th>
<th>Local Lab Serum K⁺ Value (mEq/L):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3.5</td>
</tr>
<tr>
<td></td>
<td>3.5 – &lt; 3.8</td>
</tr>
<tr>
<td></td>
<td>3.8 – 5.0</td>
</tr>
<tr>
<td>Is Current RLY5016 Dose 0 g/d?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>RLY5016 Dose Unchanged</td>
</tr>
</tbody>
</table>

**Re-stabilization of RLY5016 is defined as 3 consecutive weekly visits on the same RLY5016 dose.**

---

1. At T9 (Day 57) Visit this rule will only apply to those patients, who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits.
2. 7 days since the RLY5016 dose was changed at the previous weekly/monthly maintenance visit.
3. Re-stabilization of RLY5016 is defined as 3 consecutive weekly visits on the same RLY5016 dose.
APPENDIX E (Cont’d)

RLY5016 Long-term Maintenance titration instructions will be provided by IXRS upon entry of the local lab serum potassium value. **Part 2:**

**Weekly or Monthly Visits: T9 (Day 57) through Week 51**

<table>
<thead>
<tr>
<th>Local Lab Serum K⁺ Value (mEq/L):</th>
<th>&gt; 5.0 – 5.5</th>
<th>&gt; 5.5 – &lt; 6.0</th>
<th>6.0 – &lt; 6.5</th>
<th>≥ 6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLY5016 Dose Unchanged</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is Current RLY5016 Dose 60 g/d?¹</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is Current RLY5016 Dose 60 g/d?¹</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same Day Repeat Serum K⁺</td>
<td>&lt; 6.5</td>
<td>≥ 6.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Patients who are already on maximum RLY5016 dose 60 g/d and require further up-titration, must be withdrawn from the study.
2. RLY5016 dose increase can be greater than 10 g/d if required (per Investigator’s discretion).
3. Serum K⁺ values ≥ 6.5 require same day re-test before the titration decision is made.
4. 7 days since the RLY5016 dose was changed at the previous weekly/monthly maintenance visit.
5. Re-stabilization of RLY5016 is defined as 3 consecutive weekly visits on the same dose.
APPENDIX F
END OF TREATMENT / EARLY TERMINATION FLOWCHART

RLY5016 End of Treatment / Early Termination and Follow-up instructions will be provided by IXRS upon entry of the local lab serum potassium value.

<table>
<thead>
<tr>
<th>M11/Early Termination Visit</th>
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</thead>
<tbody>
<tr>
<td>Local Lab Serum K⁺ Value (mEq/L):</td>
</tr>
<tr>
<td>≤ 5.0</td>
</tr>
<tr>
<td>Discontinue RLY5016 at this visit but continue all RAAS inhibitors for 28 days</td>
</tr>
<tr>
<td>Follow-up Visits F1, F2, F3, F4 &amp; F5 3, 7, 14, 21 &amp; 28 Days post-M11/ET, respectively</td>
</tr>
<tr>
<td>Telephone Calls every 3 months from the last study visit for up to 1 year after T0 Visit</td>
</tr>
</tbody>
</table>
STATISTICAL ANALYSIS PLAN

Relypsa, Inc.

Protocol RLY5016-205

Protocol Title: A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone

Protocol Version and Date: Original Protocol Date: 22 February 2011
Amendment Number 1: 28 June 2011
Amendment Number 2: 23 March 2012

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Prepared By: Mark Mortier
Agility Clinical, Inc.
701 Palomar Airport Road, Suite 270
Carlsbad, CA 92011

Document Version and Date: Version 1.0; 24 September 2013
1 STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor: Relypsa, Inc.

Clinical Protocol Number: RLY5016-205

Protocol Title: A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone

Document File Name: Relypsa_RLY5016-205_SAP_v1.0_24Sep2013.pdf

Document Version and Effective Date: Version 1.0; 24 September 2013

Approved By:

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Vice President, Clinical Development
Relypsa, Inc

Date

Carol Francisco, PhD
Consultant - Biostatistician
Relypsa, Inc

Date

Mark Mortier
Director, Biostatistics
Agility Clinical, Inc.

Date

Confidential
## 2 TABLE OF CONTENTS

1 STATISTICAL ANALYSIS PLAN APPROVAL ................................................................. 2
2 TABLE OF CONTENTS .................................................................................................. 3
3 TABLE OF TABLES ........................................................................................................ 5
4 LIST OF ABBREVIATIONS ........................................................................................ 6
5 INTRODUCTION ............................................................................................................. 8
6 STUDY OBJECTIVES .................................................................................................... 9
   6.1 Primary Study Objective(s) .................................................................................. 9
   6.2 Secondary Study Objective(s) ............................................................................. 9
7 OVERALL STUDY DESIGN AND PLAN ................................................................. 10
   7.1 Study Design ......................................................................................................... 10
   7.2 Schedule of Assessments .................................................................................... 11
   7.3 Treatments ............................................................................................................ 11
   7.3.1 Treatments Administered ............................................................................. 11
   7.3.2 Method of Assigning Subjects to Treatment Groups ...................................... 13
8 Efficacy and Safety Variables .................................................................................... 13
   8.1 Primary Variables ............................................................................................... 13
   8.1.1 Treatment Initiation Period (TIP) Primary Efficacy Variable ....................... 13
   8.1.2 Long-Term Maintenance Period (LTMP) Primary Safety Variable ............ 14
   8.2 Efficacy Variables ............................................................................................... 14
   8.2.1 Treatment Initiation Period (TIP) Secondary Efficacy Variables ................. 14
   8.2.2 Long-Term Maintenance Period (LTMP) Efficacy Variables ....................... 15
   8.3 Safety Parameters ............................................................................................... 16
   8.3.1 Adverse Events (AEs) .................................................................................... 16
   8.3.2 Blood Laboratory Safety Tests ...................................................................... 17
   8.3.3 Urinalysis ........................................................................................................ 18
   8.3.4 Urine Albumin and Creatinine, Urine Albumin-to-Creatinine Ratio ............... 18
   8.3.5 Urine Pregnancy Test ..................................................................................... 18
   8.3.6 Abnormal Laboratory Tests .......................................................................... 18
   8.3.7 Resting Heart Rate and Sitting Blood Pressure ............................................ 18
   8.3.8 Physical Examination ..................................................................................... 18
   8.3.9 Electrocardiogram (ECG) ............................................................................. 19
   8.3.10 Estimated Glomerular Filtration Rate (eGFR) ............................................... 19
9 DATA QUALITY ASSURANCE .................................................................................. 19
10 STATISTICAL METHODS .......................................................................................... 20
   10.1 Analysis Populations ......................................................................................... 20
   10.1.1 Safety Population .......................................................................................... 20
   10.1.2 Intent-to-Treat (ITT) Population ................................................................ 20
   10.1.3 Per-Protocol (PP) Population ...................................................................... 20
   10.2 General Methodology ....................................................................................... 20
   10.2.1 General Considerations ............................................................................... 20
   10.2.2 Visit Windows .............................................................................................. 21
   10.2.3 Data Handling Rules .................................................................................... 22
   10.3 Interim Analysis ................................................................................................. 23
3 TABLE OF TABLES

Table 1: List of Abbreviations .................................................................................................................6
Table 2: Comparison of Investigational Drug Nomenclature and Doses for Phase 2 vs. Phase 3 Clinical Studies ..................................................................................................................9
Table 3: Visit Windows ..................................................................................................................................21
## 4 LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI(s)</td>
<td>Angiotensin-converting enzyme inhibitor(s)</td>
</tr>
<tr>
<td>ACR</td>
<td>albumin to creatinine ratio</td>
</tr>
<tr>
<td>ADMA</td>
<td>asymmetric dimethylarginine</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>apoA-IV</td>
<td>apolipoprotein A-IV</td>
</tr>
<tr>
<td>ARB(s)</td>
<td>angiotensin II receptor blocker(s)</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type (or brain) natriuretic peptide</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>cm</td>
<td>centimeters</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CT-proAVP</td>
<td>C-terminal provasopressin</td>
</tr>
<tr>
<td>CT-proET-1</td>
<td>C-terminal pro-endothelin-1</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ET</td>
<td>early termination</td>
</tr>
<tr>
<td>FGF23</td>
<td>fibroblast growth factor 23</td>
</tr>
<tr>
<td>F1</td>
<td>fluoride</td>
</tr>
<tr>
<td>g/d</td>
<td>grams per day</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
</tr>
<tr>
<td>IVRS</td>
<td>interactive voice response system</td>
</tr>
<tr>
<td>IWRS</td>
<td>interactive web response system</td>
</tr>
<tr>
<td>K+</td>
<td>potassium</td>
</tr>
<tr>
<td>kg</td>
<td>kilograms</td>
</tr>
<tr>
<td>kg/m²</td>
<td>kilograms per meters squared</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>KIM-1</td>
<td>kidney injury molecule 1</td>
</tr>
<tr>
<td>LS</td>
<td>least-square</td>
</tr>
<tr>
<td>LTMP</td>
<td>Long-Term Maintenance Period</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mEq/L</td>
<td>milliequivalents per liter</td>
</tr>
<tr>
<td>Mg⁺</td>
<td>magnesium</td>
</tr>
<tr>
<td>mg/d</td>
<td>milligrams per day</td>
</tr>
<tr>
<td>mg/dL</td>
<td>milligrams per deciliter</td>
</tr>
<tr>
<td>mITT</td>
<td>modified Intent-to-Treat Population</td>
</tr>
<tr>
<td>mL/min/1.73m²</td>
<td>milliliters per minute per 1.73 meters squared</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimeters of mercury</td>
</tr>
<tr>
<td>MMRM</td>
<td>mixed model for repeated measures</td>
</tr>
<tr>
<td>MR-proADM</td>
<td>midregional pro-adrenomedullin</td>
</tr>
<tr>
<td>MR-proANP</td>
<td>midregional pro-atrial natriuretic peptide</td>
</tr>
<tr>
<td>msec</td>
<td>milliseconds</td>
</tr>
<tr>
<td>NGAL</td>
<td>neutrophil gelatinase-associated lipocalin</td>
</tr>
<tr>
<td>PP</td>
<td>Per-Protocol</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>TIP</td>
<td>Treatment Initiation Period</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
5 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Relypsa, Inc. Protocol RLY5016-205 (A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical principles applied in the design and planned analyses of this study are consistent with the International Conference on Harmonization (ICH) guideline E9 (Statistical Principles for Clinical Trials) (1).

This SAP will be finalized prior to data analysis and before database lock to provide full details to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR.

During clinical development, reference to the investigational drug (RLY5016) changed. The calcium form of the polymer was used to describe the dose of investigational drug in all of the Phase 1 and Phase 2 clinical studies, including Study RLY5016-205. For Phase 3 and all future clinical studies of RLY5016, the active polymer anion moiety (patiromer) will be used to describe the dose of investigational drug. For consistency with Phase 3 nomenclature, for the analyses described in this SAP and the clinical study report for Study RLY5016-205, the active polymer anion moiety (patiromer) nomenclature will be used when referring to the dose of investigational drug. A comparison of nomenclature using the calcium form of the polymer and nomenclature using the active polymer anion moiety (patiromer) is shown in Table 2.
Table 2: Comparison of Investigational Drug Nomenclature and Doses for Phase 2 vs. Phase 3 Clinical Studies

<table>
<thead>
<tr>
<th>Drug Product Names</th>
<th>Phase 2 Clinical Studies</th>
<th>Phase 3 Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RLY5016 Powder for Suspension, 5 g</td>
<td>RLY5016 for Oral Suspension, 4.2 g patiromer</td>
</tr>
<tr>
<td></td>
<td>(patiromer calcium)</td>
<td></td>
</tr>
<tr>
<td>Unit Dose</td>
<td>5 g RLY5016</td>
<td>4.2 g patiromer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Doses</td>
<td>RLY5016 (expressed as the calcium form of the</td>
<td>RLY5016 (expressed as the anion form [active</td>
</tr>
<tr>
<td></td>
<td>polymer):</td>
<td>moiety] of the polymer [patiromer]):</td>
</tr>
<tr>
<td></td>
<td>10 g</td>
<td>8.4 g</td>
</tr>
<tr>
<td></td>
<td>20 g</td>
<td>16.8 g</td>
</tr>
<tr>
<td></td>
<td>30 g</td>
<td>25.2 g</td>
</tr>
<tr>
<td></td>
<td>40 g</td>
<td>33.6 g</td>
</tr>
<tr>
<td></td>
<td>50 g</td>
<td>42.0 g</td>
</tr>
<tr>
<td></td>
<td>60 g</td>
<td>50.4 g</td>
</tr>
</tbody>
</table>

6 STUDY OBJECTIVES

6.1 Primary Study Objective(s)

The primary objective of this study is to determine the optimal starting dose of RLY5016 in treating hyperkalemia in subjects with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone.

6.2 Secondary Study Objective(s)

The secondary objectives of this study are:

- To determine the efficacy of RLY5016 in treating hyperkalemia in subjects with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone;

- To determine the safety of RLY5016 in treating hyperkalemia in subjects with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone; and

- To evaluate the chronic use of RLY5016.
7 OVERALL STUDY DESIGN AND PLAN

7.1 Study Design

This is an open-label, randomized, dose ranging study to determine the optimal starting dose, efficacy and safety of RLY5016 in treating hyperkalemia in approximately 300 hypertensive subjects with nephropathy due to type 2 diabetes mellitus (T2DM) receiving ACEI and/or ARB drugs, with or without spironolactone.

Upon successful completion of screening evaluations at the Screening Visit (S1):

- **Non-hyperkalemic subjects** (local lab serum K⁺ 4.3 – 5.0 mEq/L at S1) enter the Run-In Period of up to 4 weeks. At the Initial Run-In Visit (R0) subjects with local lab serum K⁺ 4.5 – 5.0 mEq/L discontinue current ACEI and/or ARB drug and start losartan 100 mg/day (mg/d) (Cohort 1). Cohort 2 subjects remain on current ACEI and/or ARB drugs and start spironolactone 25 mg/d at the R0 Visit.

- **Hyperkalemic subjects** (confirmed local lab serum K⁺ > 5.0 – < 6.0 mEq/L at S1 or R0) continue their current ACEI and/or ARB drug dose and any other antihypertensive medication and start RLY5016 treatment (T0) without entering the Run-In Period (Cohort 3).

At the first occurrence of serum K⁺ > 5.0 – < 6.0 mEq/L during the Run-In Period, subjects from Cohorts 1 and 2 are randomized to a starting dose of RLY5016 according to their baseline (T0 Visit) serum potassium value. Subjects with baseline serum K⁺ > 5.0 – 5.5 mEq/L are randomized to either: 10 g/d (8.4 g/d patiromer), 20 g/d (16.8 g/d patiromer), or 30 g/d (25.2 g/d patiromer) starting dose of RLY5016 (1:1:1 ratio). Subjects with baseline serum K⁺ > 5.5 – < 6.0 mEq/L are randomized to either: 20 g/d (16.8 g/d patiromer), 30 g/d (25.2 g/d patiromer) or 40 g/d (33.6 g/d patiromer) starting dose of RLY5016 (1:1:1 ratio).

In Cohort 3, hyperkalemic subjects with baseline serum K⁺ > 5.0 – 5.5 mEq/L are randomized to either: 10 g/d (8.4 g/d patiromer), 20 g/d (16.8 g/d patiromer), or 30 g/d (25.2 g/d patiromer) starting dose of RLY5016 (1:1:1 ratio); while hyperkalemic subjects with baseline serum K⁺ > 5.5 – < 6.0 mEq/L are randomized to either: 20 g/d (16.8 g/d patiromer), 30 g/d (25.2 g/d patiromer) or 40 g/d (33.6 g/d patiromer) starting dose of RLY5016 (1:1:1 ratio).

The study has two RLY5016 treatment periods: a Treatment Initiation Period (TIP) for 8 weeks, followed by a 44-week Long-Term Maintenance Period (LTMP) which allows treatment with RLY5016 for up to one year. During the TIP, subjects randomized to RLY5016 treatment on Day 1 (T0 Visit) have study visits scheduled on Days 3, 8, 15, 22, 29, 36, 43, 50, and 57 (T9 or Week 8 Visit). Subjects completing the 8-week TIP continue in the LTMP with at least 11 scheduled Monthly Visits (M1-M11/early
termination [ET]) 4 weeks apart. During the LTMP, visits may occur more frequently if RLY5016 dose adjustment is necessary.

During scheduled study visits, the RLY5016 dose may be adjusted according to the corresponding titration algorithm (see section 3.5.2 and 3.6.2 of the clinical study protocol) designed to maintain an individual’s serum potassium value in the target range based on local laboratory data.

Serum potassium is measured at every study visit and dosing decisions are based on local lab results. To minimize the variance in serum potassium results, and avoid hemolysis of samples, specimen collection and handling must strictly follow specific instructions provided in the Laboratory Manual. Serum potassium samples (local and central lab) should be collected at approximately the same time in the morning for the same subject at ALL Study Visits (including any Mandatory Safety Visits and any Unscheduled Visits).

After RLY5016 discontinuation and depending on the final serum potassium level, subjects either return for 2 follow-up visits within 1 week (F1 and F2) or 5 follow-up visits within 4 weeks (F1 – F5).

Safety assessments include the incidence and severity of adverse events (AEs), clinical laboratory variables, serum fluoride, vital signs (systolic and diastolic blood pressure, and heart rate) and electrocardiogram (ECG) variables.

7.2 Schedule of Assessments

For the complete schedule of assessments, refer to Appendix A of the clinical study protocol.

7.3 Treatments

7.3.1 Treatments Administered

7.3.1.1 Investigational Product: RLY5016

Investigational product (RLY5016) is stabilized with sorbitol and is provided as a powder for oral suspension formulated with xanthan gum. RLY5016 is packaged in sachets (5 grams per sachet) with appropriate labeling. The individual sachets are assembled as a kit for dispensing.

Subjects begin taking RLY5016 on the evening of Day 1 (after the T0 Visit). The starting RLY5016 dose is randomly assigned based on baseline local lab serum potassium and then it may be adjusted based on local lab serum potassium values and according to the corresponding titration algorithm described in Sections 3.5.2 and 3.6.2 of the clinical study protocol. If the RLY5016 dose is adjusted, subjects start the new dose in the evening of the titration day. The minimum dose of RLY5016 is 0 g/d (no RLY5016
dispensed) and the maximum dose is 60 g/d (50.4 g/d patiromer). Subjects take the daily
dose of RLY5016 orally in equally divided doses twice a day with their regular meals
(breakfast and dinner). Meals should be consumed at approximately the same time each
day. RLY5016 may be taken for up to one year.

7.3.1.2 Losartan

Losartan is a marketed product and is provided and supplied by Relypsa from an
approved manufacturer.

Losartan is taken orally once daily in the morning. Losartan treatment is initiated the
next morning following the R0 Visit in subjects who receive losartan 100 mg/d (Cohort
1). The dose of losartan must remain at 100 mg/d during the Run-In, Treatment Initiation,
Long-Term Maintenance, and Follow-up (if applicable) Periods. Losartan may be taken
for up to 60 weeks (including follow-up period) until its discontinuation.

7.3.1.3 Spironolactone

Spironolactone is a marketed product and is provided and supplied by Relypsa from an
approved manufacturer.

Spironolactone is taken orally once daily at approximately the same time each day. The
spironolactone 25 mg/d treatment may be initiated during the Run-In Period, in which
case the first spironolactone dose should be taken the next morning, and may be
subsequently increased up to 50 mg/d before the T0 Visit or during the LTMP. If the
spironolactone dose is adjusted, subjects start the new dose the next morning following
the dose adjustment visit. Spironolactone may be taken for up to 60 weeks (including
follow-up period) until its discontinuation.

The dose of spironolactone during the RLY5016 TIP remains the same as it was at the
Baseline T0 Visit, except for those subjects who develop symptomatic hypotension or
SBP < 110 mmHg at any time during the study while on spironolactone, the
spironolactone dose should be reduced in half: from 50 to 25 mg/d or from 25 mg/d to 25
mg every other day. If blood pressure continues to remain uncontrolled, non-RAAS
inhibitor antihypertensive treatments should either be removed or their doses reduced.
The dose of losartan or pre-study ACEI and or/ARB (whichever applies) should remain
unchanged. Once blood pressure returns to normal the spironolactone dose may be
increased to a maximum dose of 50 mg/d, at the Investigator’s discretion.

During the Long-Term LTMP, spironolactone may be started at 25 mg/d or increased up
to 50 mg/d (if needed) for blood pressure control.

The Treatment Initiation T0 Visit (Baseline, Day 1) takes place when the subject
develops serum K⁺ > 5.0 – < 6.0 mEq/L during the Run-In Period (Cohorts 1 and 2) OR
at either the S1 or the R0 Visit (Cohort 3).
7.3.2 Method of Assigning Subjects to Treatment Groups

Eligible subjects are assigned to one of two RLY5016 treatment strata:

- **Stratum 1**: Subjects with serum K⁺ > 5.0 – 5.5 mEq/L are randomized in a 1:1:1 ratio to receive one of the following RLY5016 starting doses within each study cohort:
  - 10 g/d (8.4 g/d patiromer)
  - 20 g/d (16.8 g/d patiromer)
  - 30 g/d (25.2 g/d patiromer)

- **Stratum 2**: Subjects with serum K⁺ > 5.5 – < 6.0 mEq/L are randomized in a 1:1:1 ratio to receive one of the following RLY5016 starting doses within each study cohort:
  - 20 g/d (16.8 g/d patiromer)
  - 30 g/d (25.2 g/d patiromer)
  - 40 g/d (33.6 g/d patiromer)

After randomization to the starting RLY5016 dose all subjects initiate treatment with RLY5016 on the evening of the Day 1 visit.

This is an open-label study in which the investigational study staff, subjects, and the study sponsor are unblinded to treatment assignment. There is no control arm in this study; all subjects receive open-label active treatment (RLY5016). An open-label study is a commonly used design to evaluate the titration and safety of an investigational product.

Randomization to RLY5016 doses is performed using an interactive voice or web response system.

8 EFFICACY AND SAFETY VARIABLES

8.1 Primary Variables

8.1.1 Treatment Initiation Period (TIP) Primary Efficacy Variable

The mean change in serum potassium from baseline (T0) to Week 4 or prior to the initiation of RLY5016 dose titration (if occurs before Week 4) will be considered as the primary efficacy variable.
8.1.2 Long-Term Maintenance Period (LTMP) Primary Safety Variable

The frequency and severity of AEs during the LTMP of the trial will be the primary safety variable.

8.2 Efficacy Variables

8.2.1 Treatment Initiation Period (TIP) Secondary Efficacy Variables

Efficacy will also be assessed by the following measures during the TIP:

- Mean change in serum potassium from baseline (T0) to Week 8 or prior to the initiation of RLY5016 dose titration;
- Mean change in serum potassium from baseline (T0) to post-baseline visits;
- Time to first serum K⁺ in the range of 4.0 – 5.0 mEq/L;
- Mean change in serum potassium from end of RLY5016 treatment to follow-up visits, for subjects who discontinue the study during or at the end of the TIP;
- Proportion of subjects who maintain serum K⁺ in the range of 3.5 – 5.5 mEq/L by visit and during the entire TIP;
- Proportion of subjects who maintain serum K⁺ in the range of 4.0 – 5.0 mEq/L by visit and during the entire TIP;
- Proportion of subjects who discontinue from the study due to high serum potassium withdrawal criteria;
- Proportion of subjects maintaining the starting RLY5016 dose at Weeks 4 and 8;
- Proportion of subjects requiring RLY5016 titration;
- Proportion of subjects achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by end of Week 8;
- Time to first RLY5016 titration;
- Mean number of RLY5016 titrations;
- Mean change in blood pressure from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Weeks 4 and 8 (summarized over all cohorts by randomized starting dose and separately by Cohorts 1 and 2 combined, and Cohort 3);
• Mean change in urine albumin to creatinine ratio (ACR) from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Weeks 4 and 8 (summarized by Cohorts 1 and 2 combined, and Cohort 3);

• Proportion of subjects with ≥ 35% reduction in urine ACR from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Weeks 4 and 8 (summarized by Cohorts 1 and 2 combined, and Cohort 3);

• Proportion of subjects with urine ACR ≥ 500 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve ACR < 500 mg/g at Weeks 4 and 8 (summarized by Cohorts 1 and 2 combined, and Cohort 3); and

• Proportion of subjects with urine ACR ≥ 300 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve ACR < 300 mg/g at Weeks 4 and 8 (summarized by Cohorts 1 and 2 combined, and Cohort 3).

8.2.2 Long-Term Maintenance Period (LTMP) Efficacy Variables

Efficacy will be assessed by the following measures during the LTMP:

• The interpolated time serum potassium concentrations stay within the target range of 3.8 to 5.0 mEq/L over the duration of the LTMP of the trial;

• Proportion of subjects with serum potassium values below, within, and above various ranges by visit;

• Mean change in serum potassium from baseline (T0) to post-baseline visits;

• Mean change in serum potassium from end of RLY5016 treatment to follow-up visits, for subjects who discontinue the study drug during the TIP or LTMP;

• Mean change in serum potassium from end of RLY5016 treatment to follow-up visits, for subjects who discontinue the study drug during or at the end of the LTMP;

• Proportion of subjects who discontinue from the study due to high serum potassium withdrawal criteria;

• RLY5016 doses by visit;

• Number and type of RLY5016 titrations by visit;

• Mean change in blood pressure from R0 (Cohorts 1 and 2) or T0 (Cohort 3) visit to months 6 and 12 (summarized over all cohorts by randomized starting dose and separately by Cohorts 1 and 2 combined, and Cohort 3);
• Mean change in estimated glomerular filtration rate (eGFR) from R0 (Cohorts 1 and 2) or T0 (Cohort 3) visit to months 6 and 12 (summarized over all cohorts by randomized starting dose and separately by Cohorts 1 and 2 combined, and Cohort 3);

• Mean change in urine albumin to ACR from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to months 6 and 12 (summarized by Cohorts 1 and 2 combined, and Cohort 3);

• Proportion of subjects with ≥ 35% reduction in urine ACR from R0 (Cohorts 1 and 2) or T0 (Cohort 3) at months 6 and 12 (summarized by Cohorts 1 and 2 combined, and Cohort 3);

• Proportion of subjects with urine ACR ≥ 500 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve ACR < 500 mg/g at months 6 and 12 (summarized by Cohorts 1 and 2 combined and Cohort 3); and

• Proportion of subjects with urine ACR ≥ 300 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve ACR < 300 mg/g at months 6 and 12 (summarized by Cohorts 1 and 2 combined and Cohort 3).

8.3 Safety Parameters

Safety and tolerability will be assessed by the incidence and severity of AEs, clinical laboratory measurements, serum fluoride, vital signs, and ECG parameters. Other safety outcome measures are:

• Proportion of subjects who meet < 3.5 mEq/L serum potassium withdrawal criteria.

• Incidence of hypomagnesemia (serum magnesium < 1.4 mg/dL, < 1.0 mg/dL, and change from baseline ≥ 0.4 mg/dL).

• Incidence of cardiovascular events and renal events

• Mean change from baseline in hemoglobin A1C to months 6 and 12

8.3.1 Adverse Events (AEs)

AEs which are reported, observed, or elicited by indirect questioning are collected from the time of signing the informed consent and throughout the study until the last study visit. Whenever possible, any related AE or serious AE that is ongoing at the last study visit is followed until it resolves or becomes stable.
8.3.2 Blood Laboratory Safety Tests

All laboratory tests specified in the Schedule of Events (Appendix A of the clinical study protocol) and in the Listing of Laboratory Assays (Appendix B of the clinical study protocol) are performed by central labs. In addition to central lab assessments, local labs perform serum potassium measurements at all study visits.

Serum potassium (local and central lab) should be collected at approximately the same time in the morning for the same subject at ALL Study Visits (including Mandatory Safety Visit and any Unscheduled Visit). Serum potassium is measured at every study visit and dosing decisions are based on local lab results. To minimize the variance in serum potassium results, and avoid hemolysis of samples, specimen collection and handling must strictly follow specific instructions provided in the Laboratory Manual.

Serum Chemistry

A central lab sample is collected at the following visits: Screening (S1), Baseline T0 (Day 1), T3 (Day 15), T5 (Day 29), T7 (Day 43), T9 (Day 57), all LTMP Visits (M1 Week 12 - M11 Week 52/ET), F2 (7-Day Follow-up), F5 (28-Day Follow-up) and at any Unscheduled Visit. Serum magnesium is measured as a part of the serum chemistry panel. Subjects with a serum magnesium below 1.8 mg/dL at any time during the study should be treated per standard of care.

In addition to a central lab aliquot (full serum chemistry panel), another serum aliquot is processed by the local lab for ALT, AST, serum magnesium, and serum creatinine assays only at the Screening (S1) Visit for subjects whose screening serum K+ > 5.0 – < 6.0 mEq/L.

Hemoglobin A1c (central lab) is collected at Screening S1 Visit, T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36) and M11 (Week 52 or ET) Visits.

Hematology (central lab) is collected at Screening (S1), Baseline T0 (Day 1), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36) and M11 (Week 52 or ET) Visits.

Serum pregnancy test (central lab) is performed at Screening (S1), Baseline T0 (Day 1), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36), and M11 (Week 52 or ET) for females of child-bearing potential only.

Serum fluoride (central lab) is collected at Baseline T0 (Day 1), T5 (Day 29), T9 (Day 57), M4 (Week 24), and M11 (Week 52 or ET) Visits.

Detailed sample collection, handling, processing, and shipment instructions are provided in the Laboratory Manual.
8.3.3 Urinalysis

The urinalysis (central lab) is performed at Screening (S1), Baseline T0 (Day 1), T5 (Day 29), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36), and M11 (Week 52 or ET) Visits.

8.3.4 Urine Albumin and Creatinine, Urine Albumin-to-Creatinine Ratio

The urine albumin and creatinine tests (central lab) and calculation of the corresponding urine ACR values (central lab) are performed on urine collected at Screening (S1), each Run-In Visit (R0, R1, R2, and R3), Baseline T0 (Day 1), T3 (Day 15), T5 (Day 29), T7 (Day 43), T9 (Day 57), M1 (Week 12), M4 (Week 24), M7 (Week 36) and M11 (Week 52 or ET) Visits. Sites will train subjects to collect urine 1 and/or 2 days before scheduled study visits according to Section 6 and Appendix A (Schedule of Events) of the clinical study protocol.

8.3.5 Urine Pregnancy Test

All women of child-bearing potential must have negative urine pregnancy test on Baseline T0 (Day 1) before dispensation of RLY5016. This test is performed by the local lab at the Baseline T0 (Day 1) Visit only.

8.3.6 Abnormal Laboratory Tests

The Investigator monitors the laboratory test findings. If any laboratory test is abnormal during the course of the study, it is followed at the discretion of the Investigator. Abnormal laboratory tests are considered AEs if they are associated with symptoms or lead to a diagnosis, lead to discontinuation of RLY5016, require treatment or subject referral, or are clinically significant in their own right. In such cases, they must be reported on the Adverse Event Form.

8.3.7 Resting Heart Rate and Sitting Blood Pressure

Resting heart rate and sitting blood pressure is collected in triplicate and assessed at all Study Visits including any Mandatory Safety Visit, any Weekly Maintenance Visit, and at any Unscheduled Visit as detailed in Appendix A (Schedule of Events) of the clinical study protocol.

8.3.8 Physical Examination

A physical examination is performed, whenever possible, by the same member of the study staff for this protocol, at Screening (S1), Baseline T0 (Day 1), T9 (Day 57), and M11 (Week 52 or ET) Visits. This includes the physical examination of the following body areas and systems: head and neck, abdomen, chest, cardiovascular, respiratory, musculoskeletal, skin, neurological, and endocrine. Body weight will be measured at
Screening (S1), Baseline T0 (Day 1), T5 (Day 29), and T9 (Day 57), M4 (Week 24), M7 (Week 36), and M11 (Week 52 or ET) Visits. Body height is measured at the Screening (S1) Visit only. The body mass index (BMI) is calculated at Screening (S1), T9 (Day 57) and M11 (Week 52 or ET) Visits.

8.3.9 Electrocardiogram (ECG)

12-lead, resting ECGs are recorded and assessed by a qualified individual at Screening (S1), the First Run-In Visit (R0), Baseline T0 (Day 1), all Study Visits in the TIP, any Weekly Maintenance Visit, M1 (Week 12), M4 (Week 24), M7 (Week 36), M11 (Week 52 or ET), and last Follow-up Visit (F1-F5). ECGs at a Mandatory Safety Visit or Unscheduled Visit may occur at the discretion of the Investigator. Machine reported ECG intervals and any abnormal ECG findings are recorded.

8.3.10 Estimated Glomerular Filtration Rate (eGFR)

The eGFR is calculated by the central lab using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation at the following Study Visits: Screening (S1), Baseline T0 (Day 1), T3 (Day 15), T5 (Day 29), T7 (Day 43), T9 (Day 57), all monthly Study Visits in the LTMP (M1 – M11/ET), F2 (7-Day Follow-up), F5 (28-Day Follow-up) and at any Unscheduled Visit.

The Cohort 3 Screening (S1) local eGFR is calculated by the local lab using the CKD-EPI or Modification of Diet in Renal Disease equation. If the local lab does not calculate eGFR using either of these equations, Investigators should enter reported local lab serum creatinine value and subject’s age, gender, and race in the automatic eGFR calculator.

9 DATA QUALITY ASSURANCE

Report summaries will be generated using validated Base SAS® software, version 9.2 or higher, on a PC platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.
10 STATISTICAL METHODS

10.1 Analysis Populations

10.1.1 Safety Population

The Safety Population will include all randomized subjects who receive at least one dose of RLY5016. Assignment of subjects to treatment group is based on the starting dose actually received. All safety summary tables will be based on this analysis set.

10.1.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population will include all randomized subjects who received investigational product, defined as any subject who is randomized to receive one of the three starting dose levels within each cohort and received at least one dose of RLY5016. The primary and secondary efficacy analysis will be based on the ITT population.

10.1.3 Per-Protocol (PP) Population

The Per-Protocol (PP) population will include all subjects in the ITT population who are compliant with study drug, defined as taking 80-120% of the dispensed dose, and who do not have any important protocol deviations (see Section 10.6).

Sensitivity analyses of primary endpoint analysis will be based on the PP population.

10.2 General Methodology

10.2.1 General Considerations

Data will be analyzed by Agility Clinical biostatistics personnel. Statistical analyses will be reported with tables, figures, and subject data listings and presented in rich text format. Output specifications for all tables, listings and figures will be in conformance with guidelines specified by the International Conference on Harmonization (2). In general, tables and figures will be summarized by randomized starting dose within each stratum as well as for all subjects within each stratum. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined. Select summary tables will also be separated by cohort, where the three subjects that enrolled in the deactivated Cohort 2 will be included with the subjects in Cohort 1.

In general, quantitative variables will be summarized to indicate the population sample size (N), number of subjects with available data (n), mean, standard deviation, median, minimum, and maximum values. Qualitative variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted,
the denominator to determine the percentage of subjects in each category will be based on
the number of subjects with available data.

Statistical significance testing of select baseline characteristics and efficacy parameters
will be two-sided and performed using $\alpha=0.05$. P-values will be reported for all statistical
tests. Tests of interaction terms, if applicable, will be two-sided and performed using
$\alpha=0.10$.

10.2.2 Visit Windows

Analysis summarized by visit will be based on the following visit windows:

Table 3: Visit Windows

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>Scheduled Visit</th>
<th>Target Day</th>
<th>Analysis Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Day 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TIP</td>
<td>Day 3</td>
<td>3</td>
<td>2 to 5</td>
</tr>
<tr>
<td></td>
<td>Week 1</td>
<td>7</td>
<td>6 to 11</td>
</tr>
<tr>
<td></td>
<td>Week 2</td>
<td>14</td>
<td>12 to 18</td>
</tr>
<tr>
<td></td>
<td>Week 3</td>
<td>21</td>
<td>19 to 25</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>28</td>
<td>26 to 32</td>
</tr>
<tr>
<td></td>
<td>Week 5</td>
<td>35</td>
<td>33 to 39</td>
</tr>
<tr>
<td></td>
<td>Week 6</td>
<td>42</td>
<td>40 to 46</td>
</tr>
<tr>
<td></td>
<td>Week 7</td>
<td>49</td>
<td>47 to 53</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>56</td>
<td>54 to 70 (subjects who continue to the LTMP); &gt; 54 (subjects who do not continue to the LTMP)</td>
</tr>
<tr>
<td>LTMP</td>
<td>Week 12</td>
<td>84</td>
<td>71 to 98</td>
</tr>
<tr>
<td></td>
<td>Week 16</td>
<td>112</td>
<td>99 to 126</td>
</tr>
<tr>
<td></td>
<td>Week 20</td>
<td>140</td>
<td>127 to 154</td>
</tr>
<tr>
<td></td>
<td>Week 24</td>
<td>168</td>
<td>155 to 182</td>
</tr>
<tr>
<td></td>
<td>Week 28</td>
<td>196</td>
<td>183 to 210</td>
</tr>
<tr>
<td></td>
<td>Week 32</td>
<td>224</td>
<td>211 to 238</td>
</tr>
<tr>
<td></td>
<td>Week 36</td>
<td>252</td>
<td>239 to 266</td>
</tr>
<tr>
<td></td>
<td>Week 40</td>
<td>280</td>
<td>267 to 294</td>
</tr>
<tr>
<td></td>
<td>Week 44</td>
<td>308</td>
<td>295 to 322</td>
</tr>
<tr>
<td></td>
<td>Week 48</td>
<td>336</td>
<td>323 to 350</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>364</td>
<td>&gt; 351</td>
</tr>
</tbody>
</table>
The study day of each assessment will be calculated relative to the date of first dose of RLY5016 as the assessment date – RLY5016 first dose date + 1. Scheduled post-baseline results will be defined as the measurement collected on the day closest to the subject’s targeted visit date. This may include assessments originally collected at an unscheduled visit, mandatory safety visit, or mandatory maintenance visit, if relevant data is collected at that visit. If more than one usable measurement is collected within a window equidistant to a targeted visit date, the average of those measurements will be considered the scheduled post-baseline result, unless otherwise specified. For results that are categorical in nature, the earlier of the measurements will be considered if more than one is collected equidistant from the target.

Data summarized by visit during the LTMP will include a summary for both Week 52 and Week 52/ET, where applicable. The Week 52 summary will be reflective of data collected during the visit window provided in Table 3 (i.e., study day > 351). The Week 52/ET summary will be reflective of the data captured at the nominal Week 52/ET visit, as reported on the CRF, to summarize the last value reported for each subject during the LTMP.

Visit labels presented in by-subject data listing will be reflective of the actual, scheduled, visit value, as reported on the CRF. Where applicable, the calculated study day of each assessment will be presented as well. Summaries presented for scheduled follow-up visits following completion of the LTMP will be based on the nominal visit value as reported on the CRF.

10.2.3 Data Handling Rules

Efficacy and safety analyses relating to study drug administration, accountability, and compliance will incorporate the following data conventions, specific to data collected at the Day 1 (T0) Visit:

Drug Accountability CRF:

- If the response to “Total number of new and re-dispensed kit(s)” is missing, the response to “Number of kit(s) dispensed per IWRS” will be considered.
- If the response to “Number of unused sachets returned for this visit” is not recorded as zero or missing, it will be set to missing.
- If a response to “RLY5016 Titration at this visit” is reported, it will be set to missing prior to analysis and appear as “NA” in the by-subject listings.

RLY5016 Dosing Compliance CRF:

Response to the question “Was RLY5016 titrated this visit” will be considered to be missing, regardless of whether a “yes” or “no” response was indicated on the CRF.
Run-in Data Collection for Cohort 3 Subjects:

If any data are missing for subjects from Cohort 3 at the Day 1 (T0) Visit, the last available observation reported as occurring during the Screening Visit or Run-in visits (R0 – R3), as appropriate, will be utilized as relevant baseline data.

10.3 Interim Analysis

An interim data analysis was performed for this study based on study data collected from approximately 120 subjects (20 subjects per group) who completed Week 4 treatment visit or prematurely terminated study and had primary efficacy data. The mean change in central lab serum potassium from baseline to Week 4 (or prior to the initiation of RLY5016 dose titration) and its standard deviation for each treatment group was calculated based on this interim data set. These interim results were used to determine the optimal starting RLY5016 dose for each stratum for future studies.

The optimal starting dose for each stratum was determined based on key parameters including the following:

1. Mean change in serum potassium during first 4 weeks of treatment;
2. Proportion of subjects with serum K⁺ > 5.5 OR < 3.5 mEq/L at any time during the TIP;
3. Time to first RLY5016 titration and type of RLY5016 titration;
4. Number of titrations needed to maintain serum K⁺ in the range of 4.0 – 5.0 mEq/L; and
5. Adverse events, serious adverse events and adverse events leading to early termination.

The interim analysis statistical analysis plan can be found in Appendix 1.

10.4 Subject Disposition, Drug Exposure, and Compliance

Subject disposition will be summarized for all randomized subjects by randomized starting dose within each stratum, over all subjects within each stratum, and over all subjects combined. Summaries will include the number and percentage of subjects: in each analysis population, that complete the TIP, that enter the LTMP, that complete the study (including the LTMP), and that withdraw from the study early by reason for withdrawal. Reasons for withdrawal will be summarized separately for discontinuation during the TIP, discontinuation during the LTMP, and discontinuation over the entire course of the study. Subject disposition will also be summarized separately by cohort.
Extent of exposure to study treatment will be summarized for the Safety population by randomized starting dose within each stratum and by treatment period (TIP, LTMP, and over the full course of study treatment). The duration of exposure will be presented in days and calculated within each dosing period as last dose of study drug – first dose of study drug + 1. The total dose received within each treatment period will be calculated in grams as the total number of RLY5016 sachets received multiplied by 4.2. The mean daily dose will be calculated as the total dose received divided by the duration of exposure in days, within each treatment period and for the overall study. Duration of exposure, the total dose received, and the mean daily dose received will be summarized using descriptive statistics.

Compliance to the study treatment regimen will be calculated for all subjects who receive at least one dose of RLY5016. Compliance will be determined as the ratio of the number of sachets the subject actually took to the number of sachets the subject should have taken prior to discontinuation of study medication RLY5016. Compliance will be calculated separately for the TIP, the LTMP, and over the full course of study treatment dosing. Dosing compliance will be summarized using descriptive statistics by randomized starting dose within each stratum and over all subjects within each stratum. The number and percentage of subjects who are < 80% compliant and ≥ 80% compliant will also be presented.

Administration of losartan and spironolactone will be summarized by the number and percentage of subjects who remain on their assigned dose level of each study drug at each visit, through the Run-in Period, TIP, and LTMP. Results will be presented by randomized starting dose within each stratum and over all subjects within each stratum.

Prior to summarization of study drug exposure and compliance, data handling rules described in Section 10.2.3 will be incorporated.

10.5 Demographic and Baseline Characteristics

Demographic variables including age, sex, ethnicity, and race, will be summarized by randomized starting dose within each stratum, over all subjects within each stratum, and over all subjects combined for the safety population. Age will be calculated relative to date of informed consent and will be summarized using descriptive statistics. In addition, subject age will be categorized as “< 65 years of age,” “≥ 65 years of age,” and “≥ 75 years of age.” Age category, sex, ethnicity and race will be summarized with the number and percent of subjects in each parameter category. Treatment groups will be compared within each stratum using an analysis of variance (ANOVA) model for age and the generalized Fisher’s exact test to compare sex, ethnicity and race categories.

Baseline characteristics include disease history, medical history, height, weight, and body mass index (BMI). Disease history variables include time since chronic kidney disease onset (years), eGFR at Screening, chronic kidney disease stage based on eGFR at Screening, central laboratory serum potassium at Screening, urine ACR, time since type 2
diabetes mellitus diagnosis (years), hypertension diagnosis including time since diagnosis, blood pressure, heart failure including class designation, and ejection fraction. Disease history variables will be summarized by randomized starting dose within each stratum, over all subjects within each stratum, and over all subjects combined for the safety population. Continuous variables will be summarized using descriptive statistics and treatment groups will be compared within each stratum using an ANOVA model or the Wilcoxon rank-sum test, as appropriate. Categorical variables will be summarized with counts and percentages of subjects within each category and treatment groups will be compared using the generalized Fisher’s exact test.

Baseline characteristics and medical history will be summarized for the Safety population by randomized starting dose within each stratum, over all subjects within each stratum, and over all subjects combined. Height, weight, and BMI at baseline will be summarized using descriptive statistics. Frequency counts and percentages to summarize subjects reporting abnormal medical history by system organ class will be presented.

10.6 Protocol Deviations

The following deviations are considered important protocol deviations and will be summarized by randomized starting dose within each stratum, over all subjects within each stratum, and over all subjects combined, for the Safety population:

- Enrolled in violation of entry criteria, as collected at R0 or T0;
- Informed consent violations;
- On prohibited potassium-affecting medication during study participation;
- Not withdrawn from study when they met withdrawal criterion; and
- Investigational product incorrectly dispensed.

Frequency counts and percentages of subjects who experience any deviation or violation and those who experience a deviation or violation within each category will be summarized for the Safety population. Deviations and violations will be categorized prior to database lock. These important deviations will be used to determine the PP population.

10.7 Efficacy

10.7.1 Primary Efficacy Endpoint Analysis Methods

The primary efficacy parameter is the mean change in central lab serum potassium from baseline to Week 4 or prior to the initiation of RLY5016 dose titration (if occurs before Week 4). The primary analysis will be based on the ITT population.
The primary null hypothesis to be tested in this study is that the least squares estimate of the mean change in central lab serum potassium from baseline to Week 4 or prior to the initiation of RLY5016 dose titration within each RLY5016 dose group equals zero:

\[ H_0: \Delta t = 0; \]

Where \( \Delta \) represents the least squares estimate of the mean change in central lab serum potassium from baseline to Week 4 or prior to the initiation of RLY5016 dose titration and \( t \) represents each of treatment groups 10 g/d (8.4 g/d patiromer), 20 g/d (16.8 g/d patiromer) and 30 g/d (25.2 g/d patiromer) within Stratum 1 and 20 g/d (16.8 g/d patiromer), 30 g/d (25.2 g/d patiromer) and 40 g/d (33.6 g/d patiromer) within Stratum 2. The alternative hypothesis is that the change from baseline is different from zero within each of the treatment groups:

\[ H_1: \Delta t \neq 0. \]

The baseline measurement will be the last available measurement taken prior to the start of investigational product administration. Primary efficacy data obtained more than one day after the discontinuation of the last dose of investigational product will not be used in the analysis. For those subjects who require RLY5016 dose titration before Week 4, the endpoint will be the last observed data prior to the first titration. For subjects who discontinue investigational product without RLY5016 dose titration and prior to Week 4, the endpoint is the last observed data prior to termination.

A parallel lines analysis of covariance (ANCOVA) model will be used for the analysis of the primary efficacy measurement within Stratum 1 and Stratum 2. This ANCOVA model will include the treatment factor and baseline serum potassium as the covariate. The least squares estimate of the mean change of each treatment and its 95% confidence interval (CI) will be presented. A 95% CI of the pairwise difference between any two RLY5016 dose groups in the mean change of serum potassium will be constructed. A paired t-test will be used to test whether the mean change from baseline in serum potassium is different from zero for the combined group of subjects within each stratum.

\section*{10.7.2 Secondary and Other Efficacy Endpoint Analysis Methods}

\subsection*{10.7.2.1 Mean Change in Serum Potassium}

Mean change in serum potassium from baseline (T0) to Week 8, as well as to other post-baseline visits during the TIP will be analyzed using the same statistical methodologies as described for the primary efficacy endpoint in section 10.7.1. Data will be analyzed based on observed data at each visit, regardless of prior subject titrations.

Mean change in serum potassium from the end of RLY5016 treatment to follow-up visits will be summarized using descriptive statistics at each follow-up visit. Change from end of treatment to follow-up visits will be summarized separately for end of RLY5016
treatment at any point during the study, including end of treatment during or at the end of the TIP (for subjects that discontinued treatment during the TIP), and end of treatment during or at the end of the LTMP (for subjects that continued treatment into the LTMP). The end of RLY5016 treatment value during each respective treatment period will be the last available serum K+ value on (+ 1 day) or prior to the last dose received during the period. If a subject discontinues the TIP before completing the Week 8 (T9) visit, the date for the last dose of RLY5016 received during the TIP will be used as the end date of the TIP; if a subject discontinues the LTMP before completing Week 52 (M11), the date of the last dose of RLY5016 received during the LTMP will be used as the end date of the LTMP. For subjects who complete the Week 8 (T9) visit, the Week 8 visit date will be used as the end date of the TIP; for subjects who complete the Week 52 (M11) visit, the Week 52 visit date will be used as the end date of the LTMP.

Serum potassium measurements collected during the LTMP will be summarized using descriptive statistics by visit, to include the change from baseline.

Mean serum potassium and mean change from baseline in the serum potassium measurements will be plotted by randomized starting dose and study day over the entire treatment period.

10.7.2.2 Serum Potassium within Specific Ranges

Time (days) to the first serum K+ measurement in the range of 4.0 – 5.0 mEq/L during the TIP will be summarized using survival analysis techniques. Subjects who do not achieve a serum K+ measurement of 4.0 – 5.0 mEq/L during the TIP will be censored on at the date of their last serum K+ collection. The Kaplan-Meier product limit estimator of proportion of subjects who achieve a serum K+ measurement between 4.0 and 5.0 mEq/L, inclusive, will be plotted over time (days) by randomized starting dose. Descriptive summaries to include the estimated median value and 95% confidence interval will also be provided. Pairwise comparisons among each randomized starting dose within each stratum will be performed using the log rank test.

The time (days) that a subject maintains and stabilizes a serum K+ measurement in the range of 4.0 – 5.0 mEq/L and in the range of 3.5 – 5.5 mEq/L will be summarized using similar Kaplan-Meier survival analysis methods as described above. Stabilization in each respective range will be defined as the time from the first occurrence of a serum potassium measurement within range, inclusive, during the TIP to the next available serum potassium measurement that falls out of that range (to include measurements collected during the LTMP). Only subjects who achieve a serum potassium measurement within each respective range during the TIP will be considered for analysis. Subjects who exit the study without reporting a serum potassium measurement outside the range will be censored at the date of their last serum potassium collection.

The proportion of subjects with a serum K+ in the range of 3.5 – 5.5 mEq/L and 4.0 – 5.0 mEq/L will be summarized by visit during the TIP and over the entire TIP. The number
and percentage of subjects within the given ranges will be presented by randomized starting dose within each stratum and over all subjects within each stratum. Two-side 95% exact binomial confidence intervals surrounding the percentages of subjects within category, randomized starting dose, and stratum, will be presented. Dosing group comparisons will be made within each stratum using the generalized Fisher’s exact test.

The interpolated time (days) of serum K⁺ within the target range of 3.8 to 5.0 mEq/L during the LTMP will be summarized using descriptive statistics. An interval of time that a subject maintains serum potassium within the target range will be determined as the number of days from the interpolated time at which a subject’s potassium enters the target range to the interpolated day at which a subject’s potassium falls out of the target range. A subject’s total time in days of serum potassium within the target range over the course of the LTMP will be the sum of all intervals with potassium in range. The total time will also be standardized to the time (days) each subject was on study during the LTMP. The standardized interpolated time (days) of serum potassium within the target range will also be summarized using descriptive statistics.

The proportion of subjects with serum potassium concentrations within various ranges will be summarized by visit during the LTMP. Serum K⁺ ranges (mEq/L) will be categorized as:

- ≥ 6.5
- 6 to < 6.5
- > 5.5 to < 6
- > 5 to 5.5
- 3.8 to 5
- 3.5 to < 3.8
- < 3.5

The number and percentage of subjects within each range will be summarized by visit, randomized starting dose within each stratum, and over all subjects within each stratum.

10.7.2.3 RLY5016 Dosing Maintenance, Titration and Stabilization

The proportion of subjects maintaining their starting RLY5016 dose at Weeks 4 and 8 during the TIP, requiring any titration during the TIP, and achieving a stable RLY5016 dose by the end of Week 8 of the TIP will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. Dosing stabilization during
the TIP will be defined as any subject who is dispensed the same dose at the Week 6, Week 7 and Week 8 visits.

Within each stratum, pairwise comparisons will be made among randomized starting dose groups using the generalized Fisher’s exact test. Two-side 95% exact binomial confidence intervals surrounding the percentages of subjects within category, randomized starting dose, and stratum, will be presented.

The number of dosing titrations, dose escalations, and dose reductions reported during the TIP will be summarized using descriptive statistics by randomized dose group within each stratum. The number of titrations, escalations, and reductions received during the TIP will be categorized as “None,” “1,” “2,” or “> 2.” The number and percentage of subjects in each category will be summarized by randomized starting dose within each stratum and over all subjects within each stratum, for the ITT population.

Time (days) to the first dosing titration during the TIP will be summarized using survival analysis techniques. Subjects who do not experience a dosing titration will be censored at the date of their last dose of RLY5016 during the TIP. The Kaplan-Meier product limit estimator of proportion of subjects who experience a dosing titration will be plotted over time (days) by randomized starting dose. Descriptive summaries to include the estimated median value and 95% confidence interval will also be provided. Pairwise comparisons among each randomized starting dose within each stratum will be performed using the log rank test.

Dosing during the LTMP will be summarized using descriptive statistics for the mean daily dose (g/d) received, dosing titrations, dose escalations, and dose reductions by visit period (e.g., Week 8 – Week 12, Week 12 – Week 16, etc.) through Week 52. Dosing data summarized will include all doses received after the start of each visit period up to and including the date of the end of the visit period, based on the target day for each scheduled visit identified in Table 3. The number of titrations, escalations, and reductions incurred during each visit period will be categorized as “None,” “1,” “2,” or “> 2.” The number and percentage of subjects in each category will be summarized by randomized starting dose within each stratum and over all subjects within each stratum.

10.7.2.4 Change in Blood Pressure

Blood pressure is collected in triplicate at all scheduled time points. All analysis summaries by time point will consider the average of the three measurements collected at that particular time point. The baseline value will be the average of three measurements collected at T0; the value that is considered to be the measurement at the beginning of the Run-in Period will be the average of the three measurements collected R0.

Mean change in diastolic and systolic blood pressure from the beginning of the Run-in Period (R0, for Cohorts 1 and 2) or the baseline visit (T0, Cohort 3) to Week 4 and from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Week 8 will be analyzed using the same
statistical methodologies as described for the primary efficacy endpoint in section 10.7.1. Data will be analyzed by randomized starting dose based on observed data at each visit, regardless of prior subject titrations. Mean change in diastolic and systolic blood pressure during the TIP will be further summarized descriptively by cohort (Cohorts 1 and 2 combined and Cohort 3) and overall, with subjects from all strata and dosing groups combined within cohort.

Mean change in diastolic and systolic blood pressure from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Week 28 (M5), Week 52 (M11), and Week 52/ET (M11/ET) of the LTMP will be summarized using descriptive statistics by randomized starting dose within each stratum and over all subjects within each stratum. Mean change in diastolic and systolic blood pressure during the LTMP will be further summarized descriptively by cohort (Cohorts 1 and 2 combined and Cohort 3) and overall, with all subjects from all strata and dosing groups combined within cohort.

Mean diastolic and systolic blood pressure and mean change from R0 (Cohorts 1 and 2 combined) or T0 (Cohort 3) in the diastolic and systolic blood pressure measurements will be plotted by randomized starting dose and study day over the entire treatment period.

### 10.7.2.5 Change in Urine Albumin to Creatinine Ratio (ACR)

Urine ACR is scheduled for collection at S1, one day before the R0 visit, and on the day of the R0 visit. At all subsequent visits where urine ACR is schedule for collection, measurements are taken two days prior to each visit, one day prior to each visit, and on the scheduled visit day. The value that will represent the urine ACR for each subject at the beginning of the Run-in Period (i.e., R0) will be the average of the measurements collected at S1, the day prior to R0, and at the R0 visit. The value considered for all subsequent visits in analysis will be the average of the measurements collected two days prior to, one day prior to, and on the day of each respective visit of interest. This includes the value considered to represent baseline, collected up to and on T0. These averages will be determined programmatically, rather than utilizing the derived data points provided by the central laboratory or on the CRF.

Mean change in urine ACR from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Week 4 and from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Week 8 will be summarized by Cohorts 1 and 2 combined and by Cohort 3, for the ITT population.

The proportion of subjects that meet the following urine ACR criteria during the TIP will be summarized for Cohorts 1 and 2 combined and for Cohort 3:

- A $\geq$ 35% reduction in urine ACR at Weeks 4 and 8 from R0 (Cohorts 1 and 2) or T0 (Cohort 3),
- A urine ACR $\geq$ 500 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve an ACR < 500 mg/g at Weeks 4 and 8, and
- A urine ACR ≥ 300 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve an ACR < 300 mg/g at Weeks 4 and 8.

Reduction in ACR will be relative to the start of the Run-in Period for subjects in Cohort 1 and 2 combined and from the T0 for subjects in Cohort 3. Counts and percentages of subjects that meet each respective criterion will be summarized by Cohorts 1 and 2 combined and by Cohort 3, for the ITT population. Within each cohort group, two-side 95% exact binomial confidence intervals surrounding the percentages of subjects within category will be presented.

Mean change in urine ACR from R0 (Cohorts 1 and 2 combined) or T0 (Cohort 3) to Week 28 (M5), Week 52 (M11), and Week 52/ET (M11/ET) of the LTMP will be summarized using descriptive statistics by Cohorts 1 and 2 combined and by Cohort 3, for the ITT population.

In addition, the proportion of subjects that meet the following urine ACR criteria during the LTMP will be summarized for Cohorts 1 and 2 combined and for Cohort 3:

- A ≥ 35% reduction in urine ACR at Week 28, Week 52, and Week 52/ET from R0 (Cohorts 1 and 2) or T0 (Cohort 3),
- A urine ACR ≥ 500 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve an ACR < 500 mg/g at Week 28, Week 52, and Week 52/ET, and
- A urine ACR ≥ 300 mg/g at R0 (Cohorts 1 and 2) or T0 (Cohort 3) who achieve an ACR < 300 mg/g at Week 28, Week 52, and Week 52/ET.

Counts and percentages of subjects that meet each respective criterion will be summarized by Cohorts 1 and 2 combined and by Cohort 3, for the ITT population.

**10.7.2.6 Change in Estimated Glomerular Filtration Rate (eGFR)**

Mean change in eGFR from R0 (Cohorts 1 and 2) or T0 (Cohort 3) to Week 28 (M5), Week 52 (M11), and Week 52/ET (M11/ET) of the LTMP will be summarized using descriptive statistics by randomized starting dose within each stratum and over all subjects within each stratum.

**10.7.3 Statistical/Analytical Issues**

**10.7.3.1 Adjustments for Covariates**

The parallel lines ANCOVA model utilized in the analysis of the primary endpoint will include a covariate adjustment for the baseline serum potassium value. Select secondary endpoints will be analyzed similarly, with the baseline or run-in (R0) value for the response variable of interest included as a covariate.
10.7.3.2 **Handling of Drop-outs or Missing Data**

The primary efficacy endpoint is the central lab serum potassium data obtained at Week 4 or prior to the initiation of RLY5016 dose titration. For those subjects who require RLY5016 dose titration before Week 4, the endpoint is the last observed data prior to the first titration. For subjects who prematurely discontinued investigational product without RLY5016 dose titration and prior to Week 4, the endpoint is the last observed data prior to termination.

All other efficacy data will be analyzed according to observed data at the time point of interest, regardless of subject dosing titrations, by randomized starting dose.

10.7.3.3 **Interim Analysis and Data Monitoring**

An interim analysis was planned and performed as described in section 10.3. There is no plan to establish a committee to monitor data for this clinical trial.

10.7.3.4 **Multicenter Studies**

This is a multicenter study, with 43 sites enrolled globally. Efficacy data collected from all study centers will be pooled for data analysis.

10.7.3.5 **Multiple Comparisons/Multiplicity**

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. The primary objective of the study is to determine the optimal starting dose of RLY5016 and not to assess superiority between two or more treatment groups.

10.7.3.6 **Use of an “Efficacy Subset” of Subjects**

The primary analysis will be performed on the ITT population; the PP population will be utilized to test the robustness of the ITT results on the primary efficacy endpoint. The PP population will exclude subjects that meet various criteria that may impact the efficacy conclusions of the study including inclusion/exclusion violations, protocol violations, and are non-compliant with RLY5016 dosing.

10.7.3.7 **Active-Control Studies Intended to Show Equivalence**

This study does not employ and active-comparator product and is not intended to demonstrate equivalence between any two drug products.

10.7.3.8 **Examination of Subgroups**

The primary efficacy endpoint will be summarized by cohort (e.g., Cohorts 1 and 2, and Cohort 3) as well as by various subgroups of interest based on baseline and demographic categories including age (e.g., < 65 years of age and ≥ 65 years of age), gender, race, and
country. Summaries by subgroup will only be produced if there are at least 25 subjects in the category of interest.

The efficacy analysis of change from baseline in blood pressure will be summarized separately by cohort (e.g., Cohorts 1 and 2, and Cohort 3).

Additional subgroup analyses may be performed post-hoc, as appropriate.

10.8 Safety Analysis

10.8.1 Adverse Events

Treatment emergent adverse events (TEAEs) are defined as those adverse events (AEs) with onset after the first dose of RLY5016 or existing events that worsened after the first dose during the study. TEAEs will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. TEAEs will be summarized for those with onset over the entire treatment period and separately by study period as those with onset during the TIP and those with onset during the LTMP. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of RLY5016 based on the available date entries. If it cannot be determined whether a TEAE onset is during the TIP or the LTMP due to a partial date entry, the event will be considered to have onset during the TIP. Events with onset during the follow-up visits (F1 through F5) will be summarized with those occurring during the LTMP for those subjects who entered the LTMP; otherwise, they will be summarized with those occurring during the TIP.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 12.0).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Summary of subject incidence of selected AE categories of interest with onset during the entire treatment period, during the TIP, and during the LTMP;
- Subject and value-level incidence of select laboratory safety events with onset during the entire treatment period, during the TIP, and during the LTMP;
- Subject incidence of cardiovascular and renal events, based on select Standardized MedDRA Query narrow terms, during the entire treatment period, during the TIP, and during the LTMP;
Subject incidence of TEAEs with onset during the entire treatment period, during the TIP, and during the LTMP by MedDRA system organ class and preferred term;

Subject incidence of TEAEs with onset during the entire treatment period, during the TIP, and during the LTMP by MedDRA system organ class, preferred term, and severity.

Subject incidence of treatment-emergent serious adverse events (SAEs) with onset during the entire treatment period, during the TIP, and during the LTMP by MedDRA system organ class and preferred term;

Subject incidence of TEAEs leading to RLY5016 discontinuation with onset during the entire treatment period, during the TIP, and during the LTMP by MedDRA system organ class and preferred term;

Subject incidence of TEAEs related to RLY5016 with onset during the entire treatment period, during the TIP, and during the LTMP by MedDRA system organ class and preferred term;

At each level of summarization (e.g., any adverse event, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once, by randomized starting dose group. In the summary of TEAEs related RLY5016, subjects who experience an event reported as both “related” and “not related” to RLY5016 at each level of summarization (subjects experiencing at least one event, by system organ class, and by preferred term) will be counted as “related.” In the AE summaries by severity, subjects will be counted once at the highest severity reported at each level of summarization.

Adverse event data will be presented in data listings by subject, cohort, stratum, randomized starting dose, and event.

10.8.2 Clinical Laboratory Tests

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory. All data, including that collected by the local laboratories, will be included in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will be listed separately by subject, laboratory test, and unit.

10.8.2.1 Mean Values and Change from Baseline in Laboratory Results

Clinical laboratory measurements, including serum chemistry, hematology, renal function tests, and urinalysis will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. Descriptive statistics will be presented for results at each visit where parameters were scheduled to be collected during the TIP and
LTMP per the clinical study protocol. The change from baseline will also be summarized, where the baseline value is defined as the last available measurement collected prior to the start of investigational product.

10.8.2.2 Shifts from Baseline in Laboratory Results

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to post-baseline for each of the following:

- Worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study;
- Highest post-baseline value; and
- Lowest post-baseline value.

Summary results will include the count and percentage of subjects within each shift category, stratum, and randomized starting dose group.

10.8.2.3 Drug-Induced Liver Injury Criteria

The count and percentage of subjects with post-treatment laboratory measurements that meet various Drug-Induced Liver Injury criteria (as described in FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 [3]) will be summarized by treatment period (e.g., entire treatment period, TIP, and LTMP), stratum, and randomized starting dose. Specific measurements that meet these criteria will also be listed by subject, along with any adverse events with onset on the same day as the lab collection.

10.8.2.4 Magnesium

Boxplots will be generated for magnesium over time by randomized starting dose within each stratum and over all subjects within each stratum. They will include measurements of subjects while their patiromer dose is above 0 g/d. In addition, stacked bar charts will be provided to show the percentage of subjects with magnesium (Mg⁺) < 1.0 mg/dL, Mg⁺ ≥ 1.0 mg/dL to Mg⁺ < 1.4 mg/dL, and Mg⁺ ≥ 1.4 mg/dL.

Counts and percentages of subjects who have an outlying magnesium values or change while on patiromer will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. The following categories will be summarized:
Subjects with at least one serum Mg\textsuperscript{2+} value < 1.4 mg/dL;

Subjects with at least one serum Mg\textsuperscript{2+} value < 1.0 mg/dL;

Subjects with a decrease from baseline in serum Mg\textsuperscript{2+} \geq 0.4 mg/dL; and

Subjects with an increase from baseline in serum Mg\textsuperscript{2+} \geq 0.4 mg/dL.

Subjects meeting each respective criterion will be summarized by treatment period (entire course of treatment, TIP, and LTMP) and included in the summary of subject incidence of select laboratory safety events, as described in section 10.8.1.

10.8.2.5 Fluoride

Fluoride measurements, specific to those collected while subjects remain on patiromer, will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. Descriptive statistics will be presented for results at each visit where fluoride was scheduled to be collected during the TIP and LTMP per the clinical study protocol. The change from baseline will also be summarized, where the baseline value is defined as the last available measurement collected prior to the start of investigational product.

The change from baseline to Week 52 and Week 52/ET in fluoride will be summarized using descriptive statistics for those subjects with a year of study drug therapy by average daily RLY5016 dose level (\leq 25.2 g/d or > 25.2 g/d) as well as by starting eGFR category (< 30 mg/min/1.73 m\textsuperscript{2} or \geq 30 mg/min/1.73 m\textsuperscript{2}). In the summary of change from baseline in fluoride by average daily RLY5016 dose level, the average daily RLY5016 dose received within each dosing group will be reported.

Counts and percentages of subjects who have an outlying fluoride values or change while on patiromer will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. The following categories will be summarized:

- Subjects with a fluoride (Fl\textsuperscript{-}) value > 100 ng/dL at baseline;

- Subjects with a treatment emergent Fl\textsuperscript{-} value > 100 ng/dL at any time on study; and

- Subjects with a treatment emergent Fl\textsuperscript{-} value > 100 ng/dL at any time on study who did not return to \leq 100 ng/dL before end of treatment.

In addition, the total number of fluoride values collected at baseline, the total number of fluoride values collected at baseline that are > 100 ng/mL, the total number of fluoride values collected at all visits, and the total number of fluoride values collected at all visits.
that are > 100 ng/mL will be summarized by randomized starting dose within each stratum and over all subjects within each stratum.

Subjects and values, as appropriate, meeting each respective criterion will be summarized by treatment period (entire course of treatment, TIP, and LTMP) and included in the summary of select laboratory safety events, as described in section 10.8.1.

10.8.3 12-Lead Electrocardiogram (ECG)

Twelve-Lead ECG interval parameters will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. Descriptive statistics will be presented for results at each visit where parameters were scheduled to be collected during the TIP and LTMP per the clinical study protocol. The change from baseline will also be summarized, where the baseline value is defined as the last available measurement collected prior to the start of investigational product.

Twelve-lead ECG will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the last observed value during the TIP and LTMP, respectively. Summary results will include the count and percentage of subjects within each shift category, stratum, and randomized starting dose group.

Prolonged QTc intervals will be summarized as QTc measurements (msec) that are > 450, > 470, and > 500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change > 30 or > 60 relative to the baseline value. Summary results will include the percentage of subjects within each category, stratum, and randomized starting dose.

The incidence of ECG abnormalities occurring across the entire treatment period, across the TIP, and across the LTMP will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. The number and percent of patients who experience at least one ECG abnormality within each respective study period will be presented by abnormality.

10.8.4 Vital Signs

Vital sign parameter measurements will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. Descriptive statistics will be presented for results at each visit where parameters were scheduled to be collected during the TIP and LTMP per the clinical study protocol. The change from baseline will also be summarized, where the baseline value is defined as the last available measurement collected prior to the start of investigational product.
Increases and reductions in systolic and diastolic blood pressure will be classified as a “≥ 10 mmHg,” “≥ 15 mmHg,” and “≥ 20 mmHg” change for systolic blood pressure and as a “≥ 5 mmHg,” “≥ 10 mmHg,” and “≥ 15 mmHg” change for diastolic blood pressure, relative to the baseline value. The number and percentage of subjects whose blood pressure meets each of the given criteria will be summarized by randomized starting dose group for the following:

- At any post-baseline time point during the entire treatment period, during the TIP, and during the LTMP; and
- Across consecutive time points (i.e., “sustained”) during the entire treatment period, during the TIP, and during the LTMP.

Boxplots will be generated for systolic blood pressure and diastolic blood pressure over time by randomized starting dose within each stratum and over all subjects within each stratum. They will include measurements of subjects while their patiromer dose is above 0 g/d. In addition, stacked bar charts will be provided to show the percentage of subjects lower than the lowest cut point, between the low and high cut point, and higher than the highest cut point, based on the following criteria:

- Post-baseline systolic blood pressure < 110 mmHg;
- Post-baseline diastolic blood pressure < 60 mmHg;
- Post-baseline systolic blood pressure ≥ 180 mmHg; and
- Post-baseline diastolic blood pressure ≥ 110 mmHg.

Counts and percentages of subjects who have an outlying blood pressure value or change while on patiromer will be summarized by randomized starting dose within each stratum and over all subjects within each stratum. The following categories will be summarized:

- Subjects with a baseline systolic blood pressure ≥ 110 mmHg and a post-baseline systolic blood pressure < 110 mmHg;
- Subjects with a baseline diastolic blood pressure ≥ 60 mmHg and a post-baseline diastolic blood pressure < 60 mmHg;
- Subjects with a baseline systolic blood pressure <180 mmHg and a post-baseline systolic blood pressure ≥ 180 mmHg;
- Subjects with a baseline diastolic blood pressure <110 mmHg and a post-baseline diastolic blood pressure ≥110 mmHg;
• Subjects with a systolic blood pressure change (either increase or decrease) from baseline > 20 mmHg;

• Subjects with a diastolic blood pressure change (either increase or decrease) from baseline > 15 mmHg.

Subjects meeting each respective criteria will be summarized by treatment period (entire course of treatment, TIP, and LTMP) and by study visit.

10.8.5 Physical Examination

Physical exam findings will be presented in by-subject data listings by cohort, stratum, randomized starting dose, and body system.

10.8.6 Concomitant Medications

Anti-hypertensive medication use will be summarized during the entire treatment period, during the TIP, and during the LTMP, by stratum and randomized starting dose. The number and percentage of subjects who receive any anti-hypertensive medications, who have dose modifications to anti-hypertensive medications, and who have modifications in the number of anti-hypertension medications received will be summarized.

Prior and concomitant medications will be presented in by-subject data listings by cohort, stratum, randomized starting dose and medication.

10.9 Determination of Sample Size

This is a multicenter, randomized, open-label, dose ranging study designed to determine the optimal starting dose for RLY5016 in subjects with hyperkalemia, hypertension and diabetic nephropathy. This study will have approximately 300 subjects randomized (50 subjects per dose group) to ensure at least 252 subjects (42 subjects per dose group) will receive investigational product and provide primary efficacy data for data analysis assuming a 15% non-evaluable rate.

10.10 Changes in the Conduct of the Study or Planned Analyses

Section 9.5.4 (“Methods for the Analysis of Stratum 1 Efficacy Data”) and section 9.5.5 (“Methods for the Analysis of Stratum 2 Efficacy Data”) describe the following regarding the planned efficacy analysis of urine ACR measurements:

In addition, Mixed-Effect Model Repeated Measure (MMRM) model will be used to analyze natural log-transformed ACR data.

Urine ACR data will not be transformed prior to analysis and an MMRM approach will not be performed to compare treatment groups. Rather, all urine ACR data will be
summarized for Cohorts 1 and 2 combined, separately for Cohort 3, and over all cohorts, combining subjects across all randomized dosing assignments.

11 REFERENCES


APPENDIX 1: INTERIM ANALYSIS PLAN
Relypsa, Inc.

Protocol RLY5016-205

A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone

Statistical Analysis Plan

August 27, 2012

Prepared by:
Statistics Collaborative, Inc.

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Relypsa, Inc.

Statistical analysis plan: Protocol RLY5016-205

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Protocol synopsis

Background

Protocol RLY5016-205 is a phase 2, multicenter, randomized, open-label, dose ranging study to evaluate the efficacy and safety of RLY5016 in the treatment of hyperkalemia in patients with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone.

Primary efficacy objective

To determine the optimal starting dose of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone.

Secondary efficacy objective

To determine the efficacy of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone

Safety objectives

- To determine the safety of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone
- To evaluate the chronic use of RLY5016

Primary hypothesis

The primary null hypothesis to be tested in this study is that the least squares estimate of the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration within each RLY5016 dose group equals zero.
Study design

The study has two RLY5016 treatment periods: a Treatment Initiation Period (TIP) for 8 weeks, followed by a Long-Term Maintenance Period for an additional 44 weeks which allows treatment with RLY5016 for up to a total of one year (i.e., 52 weeks). Eligible non-hyperkalemic patients will start a Run-In Period of 1 to 4 weeks in duration (Cohorts 1 and 2). Eligible hyperkalemic patients will start treatment with RLY5016 immediately (Cohort 3). At the first occurrence of serum potassium ($K^+$) $> 5.0 – < 6.0$ mEq/L, eligible patients from all three cohorts will be assigned to one of two strata according to baseline serum potassium and will receive RLY5016 treatment at randomly assigned doses ranging from 10 to 40 g/day.

Study population

 Approximately 300 patients.

Study drug

RLY5016 is a non-absorbed, polymeric drug designed for the binding and removal of potassium from the gastrointestinal tract. RLY5016 will be taken orally twice daily in equally divided doses for up to 52 weeks starting on Day 1 (the evening dose only). Patients will take RLY5016 twice a day with their regular meals (breakfast and dinner). RLY5016 dose will be adjusted as needed according to the appropriate titration algorithm (Treatment Initiation or Long-Term Maintenance) starting on Day 3 and up to the Week 51 Visit. The minimum allowed dose is 0 g/d (no RLY5016 dispensed) and the maximum dose is 60 g/d.

Study outcome variables (treatment initiation period)

The primary efficacy variable is the mean change in serum potassium from baseline (T0) to week 4 or prior to the initiation of RLY5016 dose titration (if this occurs before week 4).
The secondary efficacy variables are the following:

- Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration
- Proportion of patients maintaining the starting RLY5016 dose at weeks 4 and 8
- Mean change in serum potassium from baseline (T0) to post-baseline visits
- Mean change in serum potassium from end of RLY5016 treatment to follow-up visits
- Proportion of patients requiring RLY5016 titration
- Proportion of patients achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by end of week 8
- Mean time to first serum K\(^+\) in the range of 4.0 – 5.0 mEq/L
- Mean time to first RLY5016 titration
- Mean number of RLY5016 titrations
- Proportion of patients who maintain serum potassium in the range of 3.5 – 5.5 mEq/L by visit and during the entire Treatment Initiation Period
- Proportion of patients who maintain serum K\(^+\) in the range of 4.0 – 5.0 mEq/L by visit and during the entire Treatment Initiation Period
- Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria
- Mean change in blood pressure from Run-In Visit (R0) to weeks 4 and 8
- Mean change in urine albumin to creatinine ratio (ACR) from R0 to weeks 4 and 8
- Proportion of patients with ≥ 35% reduction in urine ACR from R0 to weeks 4 and 8
- Proportion of patients with urine ACR ≥ 500 mg/g at R0 who achieve ACR < 500 mg/g at weeks 4 and 8
- Proportion of patients with urine ACR ≥ 300 mg/g at R0 who achieve ACR < 300 mg/g at weeks 4 and 8

The exploratory measurement is change in blood and urine biomarkers from R0 to T0, week 4 and week 8.
Safety assessments will include the incidence and severity of adverse events, clinical laboratory variables, serum fluoride, vital signs (systolic and diastolic blood pressure, and heart rate), and ECG variables.

Other safety outcome measures are:

- Proportion of patients who meet < 3.5 mEq/L serum K⁺ withdrawal criteria
- Incidence of hypomagnesemia (serum magnesium < 1.8 mg/dL)

Statistical methods

Analysis Population and Pooling of Investigators: The analysis population for the main analysis of the primary efficacy parameter and secondary efficacy parameters will be the intent-to-treat (ITT) population. The ITT population includes all randomized patients who received investigational product. Efficacy data collected from all study centers will be pooled for data analysis.

Significance Levels: The statistical tests used for the analysis of baseline variables and efficacy parameters will be performed at the alpha = 0.05 significance level. All tests will be two-sided.

Methods for the Analysis of Primary Efficacy Measurement: A parallel lines analysis of covariance (ANCOVA) model will be used for the analysis of the primary efficacy measurement. This ANCOVA model will include the treatment factor and stratification factors, baseline serum potassium and cohort, as covariates. The least squares estimate of the mean change of each treatment and its 95% confidence interval (CI) will be presented. A 95% CI for the pairwise difference between any two RLY5016 dose groups in the mean change of serum potassium will be constructed.

Analysis of Safety Data: Safety variables consist of adverse events, cardiovascular events, renal events, clinical laboratory test results, vital signs, clinically significant ECG findings, newly observed physical examination abnormalities, and termination data. All randomized patients who received at least one dose of RLY5016 will be included in the analysis and summaries of safety data.
Contents

1. Introduction .......................................................................................................................1
2. Study objectives ................................................................................................................1
   2.1. Hypothesis ...............................................................................................................2
3. Study description ..............................................................................................................2
   3.1. Study design ..........................................................................................................2
   3.2. Study treatments ....................................................................................................3
   3.3. Study visits and assessments .................................................................................3
   3.4. Eligibility ..............................................................................................................6
   3.5. Randomization ......................................................................................................9
   3.6. Blinding ................................................................................................................9
   3.7. Study objective and outcomes: treatment initiation period....................................10
      3.7.1. Primary objective ...........................................................................................10
      3.7.2. Secondary objectives ..................................................................................10
      3.7.3. Efficacy outcomes .......................................................................................10
      3.7.4. Safety outcomes ........................................................................................11
      3.7.5. Additional pre-specified outcomes ............................................................12
4. Analysis populations .......................................................................................................14
   4.1. Intent-to-treat population .....................................................................................14
   4.2. Modified intent-to-treat population ......................................................................14
   4.3. Safety populations ................................................................................................15
      4.3.1. Treatment initiation safety population ............................................................15
      4.3.2. Run-in safety population ..............................................................................15
   4.4. Important subgroups .............................................................................................15
5. General conventions and statistical considerations .........................................................16
   5.1. Study days .............................................................................................................17
   5.2. Baseline ................................................................................................................17
   5.3. Date of first titration .............................................................................................17
   5.4. Post-baseline visits ...............................................................................................18
5.4.1. Scheduled Day 3 and weekly visits ...........................................................18
5.4.2. Other scheduled visits ..............................................................................19
5.5. Early terminations and end date of TIP .........................................................19
5.6. Serum potassium at week 4 or prior to first RLY5016 titration .................19
5.7. Missing or incomplete data ...........................................................................20
5.8. Sample size determination and power calculation ........................................20
5.9. Software ........................................................................................................21
5.10. Pooling of investigator sites .......................................................................21
5.11. Stratification .................................................................................................22
5.12. Changes to planned analyses ......................................................................22
5.13. Safety parameters .......................................................................................22
6. Study population summaries ..........................................................................23
6.1. Patient disposition .........................................................................................23
6.2. Protocol violations ........................................................................................23
6.3. Demographics and baseline characteristics ...............................................24
6.4. Study medications and concomitant medications ........................................24
6.5. Study Medication Compliance ....................................................................25
6.6. ECG analyses ...............................................................................................25
7. Efficacy analyses .............................................................................................26
7.1. Primary efficacy outcome: mean change in serum potassium from baseline (T0) to week 4 or prior to the initiation of RLY5016 dose titration ........................................26
7.1.1. Sensitivity analysis .....................................................................................26
7.2. Secondary efficacy outcomes ......................................................................28
7.2.1. Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration ..............................................................28
7.2.2. Proportion of patients maintaining the randomized starting RLY5016 dose at weeks 4 and 8 ...........................................................................................28
7.2.3. Mean change in serum potassium from baseline (T0) to post-baseline visits ...............................................................................................................28
7.2.4. Mean change in serum potassium from end of RLY5016 to follow-up visits ...........................................................................................................28
7.2.5. Proportion of patients requiring RLY5016 titration .........................30
7.2.6. Proportion of patients achieving a stable RLY5016 dose by the end of week 8 ........................................................................................................30
7.2.7. Time to first serum K\(^+\) in the range of 4.0 – 5.0 mEq/L ..................30
7.2.8. Time to first RLY5016 titration.................................................................31
7.2.9. Mean number of RLY5016 titrations.......................................................31
7.2.10. Proportion of patients who maintain serum potassium in the range of 3.5 – 5.5 mEq/L by visit and during the entire TIP .......................31
7.2.11. Proportion of patients who maintain serum potassium in the range of 4.0 – 5.0 mEq/L by visit and during the entire TIP .........................32
7.2.12. Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria.........................................................32
7.2.13. Mean change in blood pressure from R0 to weeks 4 and 8 ..............33
7.2.14. Change in UACR from R0 to weeks 4 and 8.................................34
7.2.15. Proportion of patients with \(\geq 35\%\) reduction in UACR from R0 to week 4 and week 8 .................................................................................................34
7.2.16. Proportion of patients with UACR \(\geq 500\) mg/g at baseline (R0) who achieve ACR < 500 mg/g at week 4 and week 8 ..................................35
7.2.17. Proportion of patients with UACR \(\geq 300\) mg/g at baseline (R0) who achieve ACR < 300 mg/g at week 4 and week 8 .................................36
7.2.18. Change in biomarkers from R0 to T0, weeks 4 and 8 .....................36
7.3. Additional pre-specified outcomes .................................................................36
7.4. Efficacy exploratory analyses ..................................................................36
7.5. Sensitivity analyses: central and local laboratory values .......................37
7.6. Interim analysis ...........................................................................................37
7.7. Multiplicity ..................................................................................................37
8. Safety summaries ...........................................................................................38
8.1. Adverse events ...........................................................................................38
8.2. Deaths .................................................................................................................................39
8.3. Vital signs ..........................................................................................................................39
8.4. Physical examination .......................................................................................................40
8.5. Laboratory data .................................................................................................................40
8.5.1. Serum Magnesium Test Results .............................................................................40
8.5.2. Proportion of patients who discontinue from the study due to low serum potassium withdrawal criteria .........................................................................................41
8.5.3. Hemoglobin A1c Test Results .................................................................................41
8.5.4. Serum Fluoride Test Results ....................................................................................41
8.5.5. Worsening renal failure .............................................................................................41
8.6. Electrocardiogram Findings ..........................................................................................42
8.7. Concomitant medications ...............................................................................................42
9. References ..............................................................................................................................43
10. Appendices ..........................................................................................................................44
10.1. Appendix 1: Imputation rules .......................................................................................44
10.1.1. Adverse Event ...........................................................................................................44
10.1.2. Concomitant Medications .....................................................................................44
10.1.3. Other dates ..............................................................................................................45
10.2. Appendix 2. Treatment initiation titration flowcharts .................................................46
10.3. Appendix 3. Schedule of assessments .........................................................................49
Exhibits

Exhibit 1. Scheduled visits and assessments .................................................................4
Exhibit 2. Inclusion criteria ...........................................................................................6
Exhibit 3. Exclusion criteria .........................................................................................7
Exhibit 4. RLY5016 Treatment initiation titration flowchart (visits T0-T1),
protocol Appendix C .................................................................................................46
Exhibit 5. RLY5016 Treatment initiation titration flowchart (visits T2-T8),
protocol Appendix D .................................................................................................47
Exhibit 6. RLY5016 Treatment initiation titration flowchart (visit M11/Early
termination visit), protocol Appendix F ..................................................................48
Exhibit 7. Schedule of assessments for long-term maintenance and follow-up ..........49
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>aldosterone antagonist</td>
</tr>
<tr>
<td>ACEI</td>
<td>angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACR</td>
<td>albumin creatinine ratio</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin II receptor blockers</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>chronic kidney disease epidemiology collaboration</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ET</td>
<td>early termination</td>
</tr>
<tr>
<td>HbA1C</td>
<td>glycated hemoglobin</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
</tr>
<tr>
<td>K⁺</td>
<td>potassium</td>
</tr>
<tr>
<td>LOCF</td>
<td>last observation carried forward</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mEq/L</td>
<td>milliequivalents per liter</td>
</tr>
<tr>
<td>mg/d</td>
<td>milligrams per day</td>
</tr>
<tr>
<td>mg/g</td>
<td>milligram per gram</td>
</tr>
<tr>
<td>MITT</td>
<td>modified intent-to-treat</td>
</tr>
<tr>
<td>mL/min/1.73m²</td>
<td>milliliters per minute per 1.73 meters squared</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimeters of mercury</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
</tbody>
</table>

(continued)
## Abbreviations, continued

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>preferred term</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin angiotensin aldosterone system</td>
</tr>
<tr>
<td>RSAF</td>
<td>run-in safety population</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SCI</td>
<td>Statistics Collaborative, Inc.</td>
</tr>
<tr>
<td>SOC</td>
<td>system organ class</td>
</tr>
<tr>
<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
</tr>
<tr>
<td>TIP</td>
<td>treatment initiation period</td>
</tr>
<tr>
<td>UACR</td>
<td>urine albumin creatinine ratio</td>
</tr>
<tr>
<td>WHO</td>
<td>The World Health Organization</td>
</tr>
</tbody>
</table>
1. Introduction

This statistical analysis plan (SAP) is based on Relypsa’s Protocol RLY5016-205, dated March 23, 2012 (second amendment). Protocol RLY5016-205 is a phase 2, multicenter, randomized, open-label, dose ranging study designed to determine the optimal starting dose for RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone. The study consists of two periods: (1) treatment initiation period (TIP) through week 8 and (2) long-term maintenance period through week 52. The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the statistical methods that Statistics Collaborative, Inc. (SCI) plans to use to address the study aims related to the TIP. Statistical methods for the analysis of data collected during the long-term maintenance period will be described in a separate document.

The statistical principles applied in the design and planned analyses of this study are consistent with ICH guideline E9 (Statistical Principles for Clinical Trials) [1].

2. Study objectives

Primary efficacy objective

To determine the optimal starting dose of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone.

Secondary efficacy objectives

To determine the efficacy of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone.
Safety objectives

- To determine the safety of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone
- To evaluate the chronic use of RLY5016

2.1. Hypothesis

The primary null hypothesis to be tested in this study is that the least squares estimate of the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration within each RLY5016 dose group equals zero.

3. Study description

3.1. Study design

Protocol RLY5016-205 is a phase 2, open-label, randomized, dose ranging study to determine the optimal starting dose, efficacy and safety of RLY5016 in treating hyperkalemia in approximately 300 hypertensive patients with nephropathy due to type 2 diabetes mellitus (T2DM) receiving ace inhibitors (ACEI) and/or angiotensin II receptor blockers (ARB) drugs, with or without spironolactone.

The study consists of the following periods:

- Screening: up to 10 days (1 visit: S1)
- Run-In: up to 4 weeks (1 to 4 visits: R0 to R3)
- RLY5016 Treatment Initiation: first 8 weeks of RLY5016 treatment (a minimum of 10 visits: T0 to T9)
- Long-Term Maintenance: additional 44 weeks of RLY5016 treatment up to a total of one year (minimum of 11 additional monthly visits)
- Follow-up (after RLY5016 discontinuation): 1 week (2 visits) OR 4 weeks (5 visits) depending on the final serum potassium level. Patients who discontinue from the study will be followed up for survival status (phone calls) from the date of their last visit up until one year after their Treatment Initiation date
Upon successful completion of screening evaluations at the Screening Visit (S1):

- **Non-hyperkalemic patients** (local lab serum K$^+$ 4.3 – 5.0 mEq/L at S1) will enter the Run-In Period of up to 4 weeks. At the Initial Run-In Visit (R0) eligible patients with local lab serum K$^+$ 4.5 – 5.0 mEq/L who are taking at least one ACEI and/or ARB drug will either discontinue all ACEI and/or ARB drugs and start losartan 100 mg/d (Cohort 1) or continue the current ACEI and/or ARB drugs and start spironolactone 25 mg/d (Cohort 2).

- **Hyperkalemic patients** (confirmed local lab serum K$^+$ > 5.0 – < 6.0 mEq/L at S1 or R0) will continue their current dose of ACEI and/or ARB drug dose and any other antihypertensive medication and start RLY5016 treatment (T0) without entering the Run-In Period (Cohort 3).

3.2. **Study treatments**

RLY5016 will be taken orally twice daily in equally divided doses starting on Day 1 (the evening dose only). Patients will take RLY5016 twice a day with their regular meals (breakfast and dinner).

RLY5016 dose will be adjusted to maintain an individual’s serum potassium value in the target range based on local laboratory data according to the appropriate titration algorithm (Treatment Initiation Period [TIP] or Long-Term Maintenance). The minimum allowed dose is 0 g/d (no RLY5016 dispensed) and the maximum dose is 60 g/d. The titration algorithms for the TIP start on Day 3 and are provided in Exhibit 4 and Exhibit 5 in Appendix 2.

3.3. **Study visits and assessments**

Exhibit 1 provides the visit schedule for the run-in and treatment initiation periods. Serum potassium will be measured at every study visit and dosing decisions will be based on local lab results. Serum potassium samples (local and central lab) should be collected at approximately the same time in the morning for the same patient at all Study Visits (including any Mandatory Safety Visits and any Unscheduled Visits).
**Exhibit 1. Scheduled visits and assessments**

<table>
<thead>
<tr>
<th>Study activity</th>
<th>Study period</th>
<th>Screen</th>
<th>Run-ina</th>
<th>Baseline</th>
<th>Treatment initiation period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit</td>
<td>S1</td>
<td>R0</td>
<td>R1</td>
<td>R2</td>
</tr>
<tr>
<td></td>
<td>Day</td>
<td>Up to 10</td>
<td>run-in 0</td>
<td>run-in 7</td>
<td>run-in 14</td>
</tr>
<tr>
<td>Window, days</td>
<td>n/a</td>
<td>+10f</td>
<td>±1</td>
<td>±1</td>
<td>+10f</td>
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<td>Informed Consent</td>
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<td>Medical History</td>
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<td>Demographics</td>
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<td>Physical Examination</td>
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<td>Body Weight (and Height at S1 only)</td>
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<td>Heart Rate and Blood Pressure</td>
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<td>Serum Pregnancy Test</td>
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<td>L&amp;C</td>
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<td>Serum Fluoride</td>
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<td>IXRS Entry</td>
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<td>RLY5016 Dispensing and Titrationb</td>
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<td>Losartan/Spironolactone Dispensing</td>
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<td>Drug Accountability</td>
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<td>All Assessment</td>
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<td>Con Med Assessment</td>
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<tr>
<td>Urine ACR Supplies Dispensing</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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**CONFIDENTIAL**

Relypsa, Inc.

Protocol RLY5016-205

**RELYPSA RLY5016-205: STATISTICAL ANALYSIS PLAN**

August 27, 2012

Page 4

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61
Exhibit 1.  Scheduled visits and assessments, continued

C = Central lab testing; L&C = Both Local and Central lab testing (samples should be collected at approximately the same time in the morning for the same patient at all Study Visits including Mandatory Safety Visit and Unscheduled Visit); (X) = To be done if applicable

- If the local lab serum K⁺ is > 5.0 - < 6.0 mEq/L at the Screening (S1) Visit (confirmed by repeat blood draw), perform a local lab ALT, AST, serum magnesium, and serum creatinine to evaluate Cohort 3 eligibility
- RLY5016 randomization assignment for Cohort 3 patients is based on all applicable eligibility criteria, when either the S1 or R0 Visit converts to the T0 Visit.
- RLY5016 randomization assignment for Cohort 1 or 2 patients is based on all applicable eligibility criteria when one of the Run-In Visits (R1, R2 or R3) converts to the T0 Visit.
- Perform a spot urine ACR for all patients at S1 only. Collect urine ACR samples for R0 at two different time points: one day before the visit, and at the visit. For all other visits, collect samples at three different time points: two days before the visit, one day before the visit, and at the visit. Cohort 3 patients may have 2 or 3 urine ACR samples depending on which visit was converted to T0.
- Perform one unscheduled visit within 3 to 7 days for patients who are screen failures or enrollment failures after the initiation of losartan and/or spironolactone treatment during the Run-In Period
- Urine pregnancy test at the T0 Visit only will be performed by local laboratory
- Randomization to RLY5016 Starting Dose (serum K⁺ Stratsum 1 or 2)
- As applicable
- Mandatory Safety Visit required next day if the local lab serum K⁺ is 5.8 - < 6.2 mEq/L OR < 3.5 mEq/L at T1
- Mandatory Safety Visit required in 1-3 days
- Starting at the T9 Visit, patients will be titrated as needed according to the Long-Term Maintenance titration algorithm. Weekly Maintenance Visits may be required (see Long-Term Maintenance Schedule of Events [SOE]). Patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule
- The maximum allowed window for R0 Visit (calculated from the date of S1 Visit)
- The maximum allowed window for T0 Visit (calculated from the date of previous study visit: S1, R0, R1, R2, or R3)
3.4. **Eligibility**

Patients must meet all of the study inclusion criteria (see Exhibit 2), and must not meet any of the study exclusion criteria (see Exhibit 3).

### Exhibit 2. Inclusion criteria

<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age 30 – 80 years old at screening</td>
</tr>
<tr>
<td>2. Type 2 diabetes mellitus (T2DM) diagnosed after age 30 which has been treated with oral medications or insulin for at least one year prior to screening</td>
</tr>
<tr>
<td>3. Chronic kidney disease: eGFR $15 - 60$ mL/min/1.73m$^2$ at screening based on central lab serum creatinine measurement (except for patients with hyperkalemia at S1, whose eligibility will be assessed based on local lab eGFR value calculated using CKD-EPI or MDRD equation)</td>
</tr>
<tr>
<td>4. Urine ACR:</td>
</tr>
<tr>
<td>a. Cohorts 1 and 2: urine ACR $\geq 30$ mg/g at screening (S1) AND average urine ACR $\geq 30$ mg/g at the beginning of Run-In Period (R0) based on up to 3 ACR values obtained starting at S1 and ending at the R0 Visit</td>
</tr>
<tr>
<td>b. Cohort 3: not applicable</td>
</tr>
<tr>
<td>5. Local laboratory serum $K^+$ values of:</td>
</tr>
<tr>
<td>a. Cohorts 1 and 2: 4.3 – 5.0 mEq/L at S1; AND 4.5 – 5.0 mEq/L at R0; AND $&gt; 5.0 - &lt; 6.0$ mEq/L at randomization to RLY5016 (Baseline, T0 Visit)</td>
</tr>
<tr>
<td>b. Cohort 3: $&gt; 5.0 - &lt; 6.0$ mEq/L at S1 OR at R0 after same day confirmation</td>
</tr>
<tr>
<td>6. Must be receiving an ACEI and/or ARB for at least 28 days prior to screening</td>
</tr>
<tr>
<td>7. Any patient with a history of hypertension must have average SBP $&gt; 130 - \leq 180$ mmHg AND average DBP $&gt; 80 - \leq 110$ mmHg (sitting) at both screening and R0 (as applicable). While Cohorts 1 and 2 patients must have a diagnosis of hypertension to be enrolled in the study, Cohort 3 patients without a history of hypertension can be enrolled.</td>
</tr>
<tr>
<td>8. Females of child-bearing potential must be non-lactating, must have a negative serum pregnancy test at screening, and must have used a highly effective form of contraception for at least 3 months before RLY5016 administration, during the study, and for one month after study completion</td>
</tr>
<tr>
<td>9. Provide their written informed consent prior to participation in the study</td>
</tr>
</tbody>
</table>
Exhibit 3. Exclusion criteria

<table>
<thead>
<tr>
<th>Patients must NOT meet ANY of the following exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>2. Central lab hemoglobin A1c &gt; 12% at S1 (except for Cohort 3 patients who are hyperkalemic at S1)</td>
</tr>
<tr>
<td>3. Emergency treatment for T2DM within the last 3 months</td>
</tr>
<tr>
<td>4. A confirmed SBP &gt; 180 mmHg or DBP &gt; 110 mmHg at any time during Screening or Run-In Period or at Baseline T0 Visit</td>
</tr>
<tr>
<td>5. Central lab serum magnesium &lt; 1.4 mg/dL (&lt; 0.58 mmol/L) at screening (Cohort 3 patients will be evaluated based on local lab serum magnesium measurement)</td>
</tr>
<tr>
<td>6. Central lab urine ACR ≥ 10000 mg/g at screening (except for Cohort 3 patients who are hyperkalemic at S1)</td>
</tr>
<tr>
<td>7. Confirmed diagnosis or history of renal artery stenosis (unilateral or bilateral)</td>
</tr>
<tr>
<td>8. Diabetic gastroparesis</td>
</tr>
<tr>
<td>9. Non-diabetic chronic kidney disease</td>
</tr>
<tr>
<td>10. History of bowel obstruction, swallowing disorders, severe gastrointestinal disorders or major gastrointestinal surgery (e.g., large bowel resection)</td>
</tr>
<tr>
<td>11. Current diagnosis of NYHA Class III or IV heart failure</td>
</tr>
<tr>
<td>12. Body mass index (BMI) ≥ 40 kg/m2</td>
</tr>
<tr>
<td>13. Any of the following events having occurred within 2 months prior to screening: unstable angina as judged by the Investigator, unresolved acute coronary syndrome, cardiac arrest or clinically significant ventricular arrhythmias, transient ischemic attack or stroke, use of any intravenous cardiac medication</td>
</tr>
<tr>
<td>14. Prior kidney transplant, or anticipated need for transplant during study participation</td>
</tr>
<tr>
<td>15. Active cancer, currently on cancer treatment or history of cancer in the past two years except for non-melanocytic skin cancer which is considered cured</td>
</tr>
<tr>
<td>16. History of alcoholism or drug/chemical abuse within 1 year</td>
</tr>
</tbody>
</table>

(continued)
17. Central lab liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] > 3 times upper limit of normal at S1 (except for Cohort 3 patients with hyperkalemia at S1, who will have local lab ALT and AST)

18. Loop and thiazide diuretics or other antihypertensive medications (calcium channel blocker, beta-blocker, alpha-blocker, or centrally acting agent) that have not been stable for at least 28 days prior to screening or not anticipated to remain stable during study participation

19. Current use of polymer-based drugs (e.g., sevelamer, sodium polystyrene sulfonate, colesevelam, colestipol, cholestyramine), phosphate binders (e.g., lanthanum carbonate), or other potassium binders, or their anticipated need during study participation

20. Current use of lithium

21. Use of potassium sparing medications, including aldosterone antagonists (AA) (e.g., spironolactone), drospirenone, potassium supplements, bicarbonate or baking soda in the last 7 days prior to screening

22. Use of any investigational product within 30 days or 5 half-lives, whichever is longer, prior to screening

23. Inability to consume the investigational product, or, in the opinion of the Investigator, inability to comply with the protocol

24. In the opinion of the Investigator, any medical condition, uncontrolled systemic disease, or serious intercurrent illness that would significantly decrease study compliance or jeopardize the safety of the patient or affect the validity of the trial results
3.5. **Randomization**

The Randomization Visit (T0) is the first visit at which a patient achieves a serum $\text{K}^+ > 5.0 - < 6.0$ mEq/L. For patients in Cohorts 1 and 2 this will occur during the Run-In Period; for patients in Cohort 3 this will occur either at Screening or at the first Run-In Period visit.

At the Randomization Visit (T0), patients will be assigned to one of the following randomization strata based on the baseline local lab serum potassium level:

- **Stratum 1**: serum $\text{K}^+$ value $> 5.0 - 5.5$ mEq/L
- **Stratum 2**: serum $\text{K}^+$ value $> 5.5 - < 6.0$ mEq/L

Patients in Stratum 1 will be randomized in a 1:1:1 allocation ratio to receive one of three RLY5016 starting doses: 10 g/d, 20 g/d, or 30 g/d within each study cohort across all study sites. Patients in Stratum 2 will be randomized in a 1:1:1 allocation ratio to receive one of three RLY5016 starting doses: 20 g/d, 30 g/d, or 40 g/d within each study cohort across all study sites.

3.6. **Blinding**

In all portions of this open-label study, patients, investigational study staff, and Relypsa will be unblinded to the randomized starting dose of RLY5016 and all titrations. SCI will not be blinded to either the randomized starting dose or any titrated dose.
3.7. Study objective and outcomes: treatment initiation period

3.7.1. Primary objective

The primary objective is to determine the optimal starting dose of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB) drugs, with or without spironolactone.

3.7.2. Secondary objectives

The secondary objectives of this study are:

- to determine the efficacy of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone;
- to determine the safety of RLY5016 in treating hyperkalemia in patients with hypertension and diabetic nephropathy receiving ACEI and/or ARB drugs, with or without spironolactone; and
- to evaluate the chronic use of RLY5016.

3.7.3. Efficacy outcomes

The primary efficacy parameter is the mean change in central lab serum potassium from baseline to week 4 or prior to the initiation of RLY5016 dose titration, whichever occurs first.

The secondary efficacy parameters for the Treatment Initiation Period (TIP) are:

1. Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration, whichever occurs first
2. Proportion of patients maintaining the starting RLY5016 dose at weeks 4 and 8
3. Mean change in serum potassium from baseline (T0) to post-baseline visits
4. Mean change in serum potassium from end of RLY5016 treatment to follow-up visits
5. Proportion of patients requiring RLY5016 titration
6. Proportion of patients achieving a stable RLY5016 dose (defined as same RLY5016 dose for 3 consecutive visits) by the end of week 8

7. Mean time to first serum K⁺ in the range of 4.0 – 5.0 mEq/L

8. Mean time to first RLY5016 titration

9. Mean number of RLY5016 titrations

10. Proportion of patients who maintain serum K⁺ in the range of 3.5 – 5.5 mEq/L by visit and during the entire TIP

11. Proportion of patients who maintain serum K⁺ in the range of 4.0 – 5.0 mEq/L by visit and during the entire TIP

12. Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria

13. Mean change in blood pressure from R0 to weeks 4 and 8

14. Mean change in urine albumin to creatinine ratio (ACR) from R0 to weeks 4 and 8

15. Proportion of patients with ≥ 35% reduction in urine ACR from R0 to weeks 4 and 8

16. Proportion of patients with urine ACR ≥ 500 mg/g at R0 who achieve ACR < 500 mg/g at weeks 4 and 8

17. Proportion of patients with urine ACR ≥ 300 mg/g at R0 who achieve ACR < 300 mg/g at weeks 4 and 8

3.7.4. Safety outcomes

Safety outcomes during the TIP include the incidence and severity of adverse events, clinical laboratory measures, serum fluoride, vital signs (systolic and diastolic blood pressure, and heart rate), and ECG variables.

Other safety outcome measures are:

- Proportion of patients who meet < 3.5 mEq/L serum K⁺ withdrawal criteria
- Incidence of hypomagnesemia (serum magnesium < 1.8 mg/dL)
3.7.5. Additional pre-specified outcomes

Additional pre-specified outcomes will be conducted for all randomized patients unless otherwise specified. The addition pre-specified outcomes for the TIP include:

1. Time to first serum K⁺ in the range of 3.8 – 5.1 mEq/L
2. Serum potassium at baseline and all scheduled post-baseline visits, including those drawn after titration (i.e., in addition to change from baseline)
3. Proportion of patients with serum potassium < 3.5 mEq/L at any time in the TIP (i.e., including but not limited to patients who meet the < 3.5 mEq/L serum K⁺ withdrawal criteria)
4. Proportion of patients with serum potassium > 5.5 mEq/L at any time in the TIP
5. Proportion of patients who maintain serum potassium in the range of 3.8 – 5.1 mEq/L by visit and during the entire TIP
6. Change in serum potassium from end of RLY5016 treatment to follow-up visits, in the subgroups of patients with local laboratory serum potassium ≤ 5.0 mEq/L or > 5.0 mEq/L at end of treatment or early withdrawal
7. Proportion of patients who develop serum potassium > 5.0 mEq/L during follow-up, in the subgroup of patients with serum potassium ≤ 5.0 mEq/L at week 8/early termination visit.
8. Number of RLY5016 titrations in patients in the subgroups of patients on maximal RAAS inhibitors or sub-maximal RAAS inhibitors at baseline (i.e., in addition to overall)
9. Incidence of serum magnesium < 1.3 mg/dL
10. Proportion of subjects with a serum potassium ≤ 5.0 mEq/L at week 8
11. RLY5016 dose at each scheduled visit

Additional pre-specified outcomes involving the run-in period include:

1. Proportion of patients with hypotension-related adverse events (hypotension, orthostatic hypotension, syncope, dizziness) from R0 through week 8
2. Proportion of patients with SBP < 120 mmHg at any time from R0 through week 8
3. Proportion of patients with a reduction in SBP of ≥ 10 mmHg at any time from R0 through to week 8
4. Proportion of patients with a reduction in DBP of ≥ 5 mmHg at any time from R0 through to week 8
5. Proportion of patients with a reduction in SBP of ≥ 10 mmHg and a reduction in DBP of ≥ 5 mmHg at any time from R0 through to week 8
6. Change in eGFR from R0 to baseline, week 4, and week 8
7. Change in eGFR from R0 to baseline, week 4, and week 8, in the subgroup of patients with eGFR <30 mL/min/1.73 m² at R0 and the subgroup of patients with eGFR ≥30 mL/min/1.73 m² at R0
8. Proportion of patients with ≥ 25% reduction in UACR from R0 to week 4 and week 8
9. Change in UACR from the start of maximal RAAS inhibitor therapy during the run-in period to TIP baseline, week 4, and week 8
10. Proportion of patients who shift from microalbuminuria (UACR ≥ 30 mg/g and ≤ 300 mg/g) to UACR < 30 mg/g, and in the opposite direction, from the start of maximal RAAS inhibitor therapy during the run-in period to week 8
11. Proportion of patients who shift from macroalbuminuria (UACR > 300 mg/g) to microalbuminuria (UACR ≥ 30 mg/g and ≤ 300 mg/g), and in the opposite direction, from the start of maximal RAAS inhibitor therapy during the run-in period to week 8

The following analyses only include patients in Cohorts 1 and 2 for all patients who enrolled in the study, regardless of whether they were randomized to RLY5016:
1. Proportion of patients who become hyperkalemic (serum potassium > 5.0 mEq/L) during the run-in period
2. Time to hyperkalemia during the run-in period
3. Change in serum potassium from the start of maximal RAAS inhibitor therapy during the run-in period to TIP baseline
4. Proportion of patients with serum potassium > 5.5 mEq/L and at any time during the run-in period
5. Proportion of patients with serum potassium > 6.0 mEq/L at any time during the run-in period

4. Analysis populations

4.1. Intent-to-treat population

The analysis population for the main analysis of the primary efficacy parameter and secondary efficacy parameters will be the intent-to-treat (ITT) population. The ITT population will include all randomized patients who received investigational product. For the main analysis of efficacy subjects will be analyzed by their randomized starting dose, regardless of the starting dose that they actually received.

4.2. Modified intent-to-treat population

Sensitivity analyses of efficacy endpoints may be based on the modified intent-to-treat (MITT) population. This population will include all randomized patients with no protocol violations or other conditions that could impact the effect of RLY5016, who were exposed to study drug during the TIP. Patients will be analyzed by their randomized starting dose.

The following patients will be excluded from the MITT population:

- Patients with one or more of the following inclusion/exclusion violations (patients in Cohorts 1 and 2 only):
  - Central laboratory eGFR < 15 mL/min/1.73m² or ≥ 60 mL/min/1.73m² at screening
  - Central laboratory urine ACR ≥ 10,000 mg/g at screening
- Patients with one or more of the following protocol violations:
  - Use of new, or change in dose of, ACEI and/or ARBs and or AAs during the treatment initiation period
  - Use of K⁺ lowering polymer-based drugs, such as sodium or calcium polystyrene sulfonate
  - Use of K⁺ sparing medications other than spironolactone (e.g., drospirenone), potassium supplements, bicarbonate, or baking soda
- Patients who are not at least 80% compliant with RLY5016
- Patients with baseline (central laboratory) serum potassium ≤ 5.0 mEq/L
- Patients who add or change the dose of spironolactone, diuretics, NSAIDS, beta blockers, or digoxin

4.3. **Safety populations**

4.3.1. *Treatment initiation safety population*

Unless otherwise stated, all randomized patients who received at least one dose of RLY5016 will be included in the analyses and summaries of safety data. For the analysis of safety, patients will be analyzed according to the dose to which they were randomized. Selected presentations will also analyze patients according to the dose they received at the time of measurement.

4.3.2. *Run-in safety population*

To examine the safety and efficacy of treatment of the run-in portion of the study, we will present safety summaries for all patients who enrolled in the study, regardless of whether they were randomized to RLY5016. The run-in safety population (RSAF) includes all patients who were screened and/or treated during the run-in period. This population will include all randomized patients in Cohorts 1 and 2 as well as those patients who failed to meet the enrollment criteria.

4.4. **Important subgroups**

Exploratory analyses will describe the effects of treatment with RLY5016 on serum K⁺ in the following subgroups: age group (65 years or older, younger than 65), sex (female, male), eGFR (CKD stages 4/5 [<30 mL/min/1.73 m²] versus stages 3 and below [≥30 mL/min/1.73m²]), with and without heart failure (HF), maximal RAAS inhibitor versus sub-maximal RAAS inhibitor, and cohort (non-hyperkalemic [Cohorts 1 and 2], hyperkalemic [Cohort 3]). Patients will be classified in subgroups using their age, sex, eGFR, HF status, and RAAS medication status at baseline.
5. General conventions and statistical considerations

In general, categorical variables will be described using numbers of patients (including the number at risk) and related percentages. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. When making statistical inference to categorical data, we will usually report either the exact binomial confidence intervals (CIs) and p-values obtained from Fisher’s exact test or the estimated proportions from logistic regression models with confidence intervals and p-values from the Wald statistic.

Continuous variables will generally be described using number of observations (n), mean, standard deviation (SD), quartiles (median, 25\textsuperscript{th}, and 75\textsuperscript{th} percentiles), minimum and maximum. CIs will be presented as appropriate. The F-test associated with the Type III sum of squares from the analysis of variance (ANOVA) or the analysis of covariance (ANCOVA) models will generally be used to infer differences among randomized dosing groups.

Unless otherwise stated, CIs will be two-sided and constructed at a 95% confidence level and hypothesis tests will be two-sided and performed at significance level alpha = 0.05.

Tabular presentations will display at least three columns of results, one for each of the three starting dose treatment regimens within each stratum. Throughout this analysis plan, the phrase “by treatment regimen” will be understood to mean the three groups within stratum described in the previous sentence.

In general, presentations will display results by randomized starting dose within strata. Other tables may present results by cohort or randomized starting dose within cohort. Safety presentations may also categorize dose based on the actual dose at the time of event. For analytical purposes the three patients enrolled in the deactivated cohort (Cohort 2) will be combined with patients in Cohort 1; all of these patients were non-hyperkalemic at screening.
5.1. **Study days**

For the majority of the analyses, study day will be calculated relative to baseline randomization day during the TIP (T0). Specifically:

\[
\text{Study day} = \text{date of visit/test/procedure} - \text{T0 date} + 1.
\]

For safety analysis during the Run-In Period, the study day will usually be calculated relative to the first day of the Run-In period (R0). Select secondary safety and efficacy measures will be calculated relative to the first day of the titrated dose or the last date of dose of RLY5016.

5.2. **Baseline**

Since patients receive their first dose of RLY5016 at the randomization visit (T0) and take their dose on the evening of that visit, the baseline measurement will be defined as the last available measurement taken prior to or on the date of randomization. The date and time of randomization will be defined by the automatically-generated IVRS data variables IVRSĐT and IVRSTM. For example, baseline serum K\(^+\) will be defined as the value for serum K\(^+\) in the central laboratory data drawn on or most recently before randomization. The randomization visit (T0) is also referred to as the day 1 visit, i.e., not day 0. SCI will not use any measurement collected after the first dose of study drug in the calculation of baseline. SCI will compare the collection date and time of the sample to the date and time of randomization as a proxy for the date and time of first dose.

If one or more measurements occur on the same date prior to or on the date of randomization, the average of all measurements will be used.

5.3. **Date of first titration**

Several study outcomes for the TIP involve date of first titration. This will be obtained from the IVRS data, because the IVRS was required in order to titrate. The date will be confirmed using the CRF data. The date of first titration will be the *earliest* system-generated date that occurs during the TIP (less than 58 days from randomization); and
contains a RLY5016 dose different from the randomized starting dose; \textit{and} pertains to RLY5016 itself, not “Spironolactone” or “Losartan”.

The value of the associated outcome of interest will be obtained as the value for the measurement made on or most recently before, but never after, the date of first titration.

5.4. \textbf{Post-baseline visits}

5.4.1. \textit{Scheduled Day 3 and weekly visits}

During the TIP outcomes measured at visits that are scheduled to occur no less frequently than weekly, such as serum potassium, blood pressure, and ECG, have a per-protocol visit window of ± 1 day from the expected visit date. Clinics adhered to the visit window where possible. The analysis values will reflect those weekly measurements as they occurred and were recorded by the clinical site, regardless of the time relative to the expected visit window. The Sponsor and the data management organization are responsible for ensuring the chronological consistency of the data and visit labels. The regularly scheduled clinic visits will include the following visits with the treatment labels for the clinic and laboratory visits:

- Day 3 (T1)
- Week 1 (T2)
- Week 2 (T3)
- Week 3 (T4)
- Week 4 (T5)
- Week 5 (T6)
- Week 6 (T7)
- Week 7 (T8)
- Week 8 (T9)

If a parameter has more than one record with the corresponding visit label on different dates, we will choose the record with earliest date of measurement. If one or more measurements occur on the same date, the latter measurement will be used. For
measurements other than serum potassium if time is not available for all records and the measurements are not all equal, we will be conservative with respect to safety and choose the worst value (e.g., higher blood pressure, lower eGFR). For serum potassium if the time on all measurements is not available we will take the highest value if any value is 5.0 mEq/L or higher; the lowest value if no values are 5.0 mEq/L or higher and at least one value is less than 3.5 mEq/L; or the average if all values are at least 3.5 mEq/L and less than 5.0 mEq/L. SCI will not consider measurements from safety visits or other unscheduled events in the calculation of scheduled Day 3 or weekly visit data.

5.4.2. Other scheduled visits

For outcomes that are scheduled to be measured less frequently than weekly, such as serum fluoride, UACR, and hemoglobin A1c, we will also use the scheduled visits as labeled and will exclude records with unscheduled or safety visit labels.

5.5. Early terminations and end date of TIP

Patients may terminate early during the TIP for hypokalemia or hyperkalemia as a result of the RLY5016 titration algorithm (see Appendix 2), or for other reasons (see Protocol section 6.5). All measurements ordinarily obtained at the week 8 (T9) visit are scheduled to be obtained at the early termination (ET) visit (see Appendix 3). A patient whose local laboratory serum potassium value at the ET visit is 5.0 mEq/L or below should attend 5 follow-up visits through an additional 28 days, while a patient whose local laboratory serum potassium value at the ET visit is > 5.0 mEq/L should attend 2 follow-up visits through an additional 7 days (see Exhibit 6 in Appendix 2). When a patient discontinues the TIP for any reason before completing the week 8 (T9) visit, we will use the last date of RLY5016 dose as the end date of the TIP. For patients who complete the week 8 (T9) visit, we will use the visit date as the end date of the TIP.

5.6. Serum potassium at week 4 or prior to first RLY5016 titration

The primary outcome is change in serum potassium from baseline to the week 4 visit or first RLY5016 dose titration, whichever occurs first. This analysis will be based on central
laboratory serum potassium values. We will define the baseline measurement as outlined in section 5.2. For patients who titrate prior to the week 4 visit, we will consider the serum potassium measurement from the most recent draw on or before the date of first RLY5016 titration regardless of visit label, as outlined in section 5.3. If a patient does not titrate before the week 4 visit, we will use the central laboratory serum potassium value for the visit as described in section 5.4.1. If the week 4 visit measure does not exist, we will select the most recent non-missing measurement of serum potassium from the central laboratory data regardless of the visit label, even if the most recent visit was made at baseline (i.e., last observation carried forward [LOCF]). Patients who discontinue prior to the week 4 visit and who have not titrated will be included in the analysis of the primary outcome. We will take the most recent non-missing measurement of serum potassium from the central laboratory data up through and including the last dose date (see section 5.5), regardless of visit label.

5.7. Missing or incomplete data

The approach defined in section 5.6 LOCF, is consistent with the protocol and the prior SAP. LOCF is the method that was used in the interim analysis from which doses to pursue in phase 3 were selected. Because the FDA has already seen those results, SCI will continue to use this approach in the main analysis of the primary endpoint and the analogous secondary efficacy endpoint at week 8.

Sensitivity analyses for these two endpoints will employ mixed model repeated measures using all scheduled data until titration, as described in section 7.5. For mixed model repeated measures analyses patients who do not have a regularly scheduled visit with the appropriate visit label will have a missing data point for that visit, and no imputation will be performed for missing values.

5.8. Sample size determination and power calculation

Sample size calculations were performed prior to SCI’s involvement in the trial.
Each stratum will have approximately 150 patients randomized in a 1:1:1 allocation ratio (50 patients per dose group) within each study cohort to ensure at least 126 patients (42 patients per dose group) will receive investigational product and provide primary efficacy data for data analysis assuming a 15% non-evaluable rate. Patients in stratum 1 will have baseline local lab serum $K^+$ value $> 5.0$ – $5.5$ mEq/L and patients in stratum 2 will have with baseline local lab serum $K^+$ value $> 5.5$ – $< 6.0$ mEq/L. A sample size of 42 patients for each RLY5016 dose group is based on an effect size of 0.5 for the primary efficacy measurement, change in serum $K^+$ from baseline to week 4 or prior to the initiation of RLY5016 dose titration. This sample size will have 90% power to detect statistically significant change at a significance level of $\alpha = 0.05$ within each dose group. The calculation is based on a two-sided one sample paired t-test, and a significance level of $\alpha = 0.05$. Assuming a 15% non-evaluable rate, approximately 150 patients are expected to be randomized in each stratum.

5.9. **Software**

Qualified statisticians and SAS programmers at SCI will perform the statistical analyses and generate the data listings, summaries, and figures using SAS Version 9.2 or higher with SAS code prepared specifically for the project in accordance with SCI’s programming standard operating procedures (SOP).

5.10. **Pooling of investigator sites**

Efficacy data collected from all study centers will be pooled for data analysis. Given that the study has many investigative sites (over 40) relative to the number of randomized subjects (over 300), analyses will not be stratified by site. All sites use the same protocol, entry criteria, data collection methods, and endpoints; sites are monitored to verify compliance with the protocol. According to Meinert (1986) [3] these criteria justify pooling results across centers.
5.11. Stratification

Patients were stratified according to the following two factors:

- Local baseline serum potassium, K^+
  - Stratum 1: Greater than 5.0 mEq/L and ≤ 5.5 mEq/L
  - Stratum 2: Greater than 5.5 mEq/L and less than 6.0 mEq/L
- Timing of hyperkalemia: Patients who entered the study on or after September 13, 2011 were also randomized within two cohorts:
  - Cohort 1: Patients who were non-hyperkalemic at screening and developed hyperkalemia during the run-in period
  - Cohort 3: Patients who were hyperkalemic at screening

The study initially included two cohorts of patients who were non-hyperkalemic at baseline, Cohort 1 and Cohort 2. Three total patients were randomized to Cohort 2 before enrollment into that cohort was deactivated and Cohort 3 was created (June 28, 2011).

5.12. Changes to planned analyses

Changes to the analyses described in this plan will be fully documented in a revised version of the plan prior to locking the study database. Changes made after locking the study database will be described in the clinical study report and characterized as “exploratory”.

5.13. Safety parameters

Safety outcomes include all adverse events (AEs), laboratory results including serum fluoride, physical examination results, vital signs, and electrocardiograms (ECGs) collected at study visits following first dose of study drug. Other safety outcome measures are hypomagnesia and withdrawal related to hypokalemia.

Adverse events are collected and reported through 7 days after discontinuation of RLY5016, if serum K^+ is > 5.0 mEq/L. Clinics report adverse events for 28 days post treatment for patients whose serum K^+ is ≤ 5.0 mEq/L at discontinuation. Because RLY5016 is not systemically absorbed, the protocol included a 7 day follow-up monitoring window for adverse events.
Survival data will be collected through phone contacts to be made every 3 months starting from the last study visit and continuing until one year after the patient’s baseline visit.

6. Study population summaries

6.1. Patient disposition

The number and percentage of patients who are randomized, receive treatment, and withdraw from the study early will be presented by country, site, randomized starting dose, cohort, and stratum. For randomized patients who withdraw early, the number and percentage withdrawing by reason will be presented. The number and percentage of patients in each analysis population will also be presented.

We will present the number of patients who enrolled, participated in the run-in phase, and failed to achieve hyperkalemia. For these patients and for all screening and enrollment failures, we will summarize the titrations and use of spironolactone, losartan, ACEI, and ARB by time.

6.2. Protocol violations

Protocol violations among randomized patients include:

- Use of new, or change in dose of, ACE-I and/or ARB’s and/or AA’s during the treatment initiation period, except for changes in spironolactone because of low blood pressure.
- Use of K⁺ lowering polymer-based drugs, such as sodium or calcium polystyrene sulfonate
- Use of K⁺ sparing medications other than spironolactone (e.g., drospirenone), potassium supplements, bicarbonate or baking soda

We will summarize the number of randomized patients with protocol violations, by violation type and combined. We will summarize the patients whose date of first dose of RLY5016 is different from the date of randomization.
6.3. **Demographics and baseline characteristics**

Patient demographics and baseline characteristics will be summarized by randomized starting dose, cohort, and stratum for patients in the TIP and by randomization status (randomized versus not randomized) in the RSAF. Information to be summarized includes age in years, gender, race, country, BMI, and weight. Age may also be presented dichotomized at 65 years old. We will provide p-values to demonstrate the effect of randomization to create treatment groups that are similar with respect to their baseline characteristics within stratum. We will use the F-test from an ANOVA to compute the p-values for continuous variables and Fisher’s exact test for categorical variables.

Disease history (particularly cardiovascular history and type 2 diabetes mellitus), ejection fraction, heart failure, baseline blood pressure, kidney function (chronic kidney disease by stage, eGFR), and medication use will be summarized by treatment group for all randomized patients for each stratum and cohort for patients in the TIP and by randomization status (randomized versus not randomized) in the RSAF.

We will use tabular and graphic presentations to illustrate the distribution of the baseline and screening central laboratory serum potassium values by stratum and cohort within stratum. We will provide listings of patients whose baseline central laboratory serum potassium values are different from the value used to define the stratum at randomization. We will provide the descriptive statistics of central laboratory serum potassium at each regularly scheduled visit during the TIP.

6.4. **Study medications and concomitant medications**

In addition to RLY5016, clinics can actively manage losartan, RAAS inhibitors, and spironolactone during the run-in period and TIP in order to control blood pressure and serum potassium. We will summarize the length of exposure to RLY5016, and where possible, these medications by the number of days and titrations during the TIP in descriptive tables by randomized starting dose and stratum for randomized patients who received at least one dose of RLY5016.
We will summarize the length of treatment of study medications (losartan, RAAS inhibitors, and spironolactone) for patients enrolled in the run-in period by cohort and randomization status (randomized versus not randomized) for all patients in the RSAF population. We will generate patient-level graphics, such as Data Mosaics©, individual patient profile plots, or AETime© presentations to graphically illustrate the time course of dosage for patients during the TIP and run-in phase.

All concomitant medications collected from screening through the end of the treatment period will be classified by preferred terms according to the World Health Organization (WHO) drug dictionary December 2010. Special groups of medications (e.g., statins, oral anti-hyperglycemics, and insulin) will be tabulated by randomized starting dose or actual dose as appropriate.

6.5. Study Medication Compliance

The RLY5016 sachet compliance rate will be calculated for all patients who received at least one dose of RLY5016 as the measurement of individual patient compliance to RLY5016. We will define compliance as the ratio of the number of sachets the patient actually took to the number of sachets the patient should have taken prior to the discontinuation of study medication RLY5016. Each patient’s compliance to RLY5016 will be calculated between clinical visits and averaged across the days in between. We will summarize compliance across all patients by time (baseline to week 4, week 5 – week 8), by cohort, and by stratum adjusted for time on study (number of patient-days). Compliance will be presented by the actual dose prescribed for a time period, as well as by randomized starting dose regardless of titration. There will be no formal inference or p-values calculated for compliance.

6.6. ECG analyses

We will summarize the ECG measures of interest in tabular form, by visit and randomized starting dose within stratum. We may summarize continuous measures by visit using box plots to demonstrate the change and distribution; we will summarize categorical variables.
using numbers and percentages. Data Mosaics© may also be used to present the time
course of select ECG events against treatment of RLY5016.

7. **Efficacy analyses**

Central lab values of serum potassium will be used as the primary measure of efficacy.
Local laboratory values may be used in supportive analyses. The main analysis of efficacy
will be performed for the ITT population. Additional analyses may be performed, e.g., for
the mITT population as defined in section 4.2.

7.1. **Primary efficacy outcome: mean change in serum potassium from baseline (T0)
to week 4 or prior to the initiation of RLY5016 dose titration**

The primary efficacy parameter is change in serum K⁺ from baseline until the week 4 visit
or RLY5016 dose titration, whichever comes first. Measurements to be used in this
analysis are described in section 5.6.

A parallel lines analysis of covariance (ANCOVA) model will be used for the analysis of
the primary efficacy measurement for each stratum. The response variable will be the
change in serum K⁺ from the baseline visit. Each ANCOVA model will include fixed
effects for the randomized starting dose, the central lab baseline serum potassium, and
cohort. The least squares estimate of the mean change in serum potassium for each
randomized starting dose and its 95% confidence interval (CI) will be presented. A 95% CI
and nominal p-value from the linear contrast of the difference between any two randomized
starting doses in the estimated mean change of serum potassium will be constructed.

We will analyze each patient according to the stratum within which he or she was
randomized to starting RLY5016 dose, regardless of the actual central laboratory serum K⁺
result.

7.1.1. **Sensitivity analysis**

To test the robustness of the results, we will construct a mixed model for repeated measures
(MM RM) within each stratum including all serum potassium measures at scheduled visits
drawn prior to the week 4 visit or the first RLY5016 dose titration, whichever occurs first. Unless otherwise specified, the MMRM will have the following characteristics:

- The response variable will be the change in serum $K^+$ from the baseline visit
- The repeated post-baseline measurement from each patient will be identified by the patient identifier (USUBJID)
- The within-patient correlation will be modeled using a heterogeneous Toeplitz structure that assumes measurements from samples taken closer together in time are more highly correlated than those taken from samples taken farther apart and does not presume equal spacing of measurements. If the model using the heterogeneous Toeplitz structure does not converge, we will use structures that are progressively more restrictive (i.e., have a smaller number of parameters to estimate), such as the homogeneous Toeplitz structure, AR(1) structure, or compound symmetry structure.
- The model will include Cohort as a categorical variable. Cohorts 1 and 2 will be combined for this analysis, because there are only three patients in Cohort 2.
- The model will contain the baseline serum potassium value as a continuous variable.
- The model will also contain the following fixed-effect covariates considered as categorical variables:
  - Randomized starting dose
  - Time (Visit)
  - Randomized starting dose-by-visit interaction.

Because time will be included in the model as a categorical variable, no restriction is imposed on the trajectory of the mean outcome over time.

We will estimate the mean effect for each starting dose and its 95% confidence interval using a linear contrast statement at the week 4 visit. We will make pairwise comparisons using linear contrasts to test the differences between dosing groups in each stratum, reporting the p-value from the F-test.
7.2. Secondary efficacy outcomes

7.2.1. Mean change in serum potassium from baseline (T0) to week 8 or prior to the initiation of RLY5016 dose titration

We will perform analysis using the methodology outlined in section 7.1 for the primary efficacy outcome, extending the visit to week 8 when deriving variables per section 5.6.

7.2.2. Proportion of patients maintaining the randomized starting RLY5016 dose at weeks 4 and 8

For the purposes of this analysis, patients will be considered to have maintained their starting randomized dose unless the IVRS data shows titration and/or the CRF data shows discontinuation before the visit of interest (week 4, week 8).

We will use logistic regression models, one model for each stratum, to estimate the probability of maintaining the randomized starting dose using a logit link function and the following covariates: randomized starting dose (where the reference category is the lowest dose in each stratum [10 g/d for stratum 1 and 20 g/d for stratum 2]) and cohort (the reference category is the combined cohorts 1 and 2). We will report the estimated proportion of patients maintaining the randomized starting dose and 95% confidence intervals obtained from the maximum likelihood estimates (Wald statistics). We will report the overall p-value among all randomized starting doses across cohorts (Wald statistics).

7.2.3. Mean change in serum potassium from baseline (T0) to post-baseline visits

We will construct a repeated measures mixed model as outlined in section 7.1 above incorporating all scheduled visits regardless of titration through week 8. We will present the results for scheduled weekly visits through week 8 by randomized starting dose within stratum and overall.

7.2.4. Mean change in serum potassium from end of RLY5016 to follow-up visits

We will construct a repeated measures mixed model for each stratum including all serum potassium measures on or after the discontinuation (“end”) of RLY5016 treatment, as
defined in section 5.5, similar to the analysis described in section 7.1.1. For patients who complete the week 8 visit, the IVRS visit date will be used at the end of treatment date and the serum potassium value at the end of RLY5016 treatment will be the week 8 value from the central laboratory data. When a patient discontinues for any reason before completing the week 8 visit the last date of RLY5016 dose marks the end of RLY5016 treatment and the serum potassium value at the end of RLY5016 treatment will be the value from the central laboratory data made on or most recently before, but never after, that date. Unless otherwise specified, the model will have the following characteristics:

- The response variable will be the change in serum K⁺ from the time of discontinuation of RLY5016 defined as the last available serum K⁺ value on or prior to the last dose.
- The repeated post-discontinuation measurement from each patient will be identified by the patient identifier (USUBJID).
- The within-patient correlation will be modeled using a heterogeneous Toeplitz structure or, if such a model does not converge, structures that are progressively more restrictive (see section 7.1.1).
- The model will include cohort as a categorical variable, described in section 7.1.1.
- The model will contain the serum potassium value at the time of discontinuation as a continuous variable.
- The model will contain the number of days the patient took RLY5016 before termination (using actual dates of use, not visit labels).
- The model will also contain the following fixed-effect covariates considered as categorical variables:
  - Randomized starting dose
  - Follow-up time (Visit)
  - Randomized starting dose-by-visit interaction.

Because time will be included in the model as a categorical variable, no restriction is imposed on the trajectory of the mean outcome over time. Follow-up time may be considered as a continuous variable with appropriate covariance structure if models
considering follow-up time as a categorical variable do not fit the data well (e.g., if there are very few F3, F4, and/or F5 visits).

We will estimate the mean overall effect across starting doses within each stratum and its 95% confidence interval using linear contrast statements.

7.2.5. Proportion of patients requiring RLY5016 titration

For the purposes of this analysis, Relypsa will consider patients to have required titration if the IVRS data indicates a titration of RLY5016 during the TIP. We will perform these analyses using the methodology described in section 7.2.2.

7.2.6. Proportion of patients achieving a stable RLY5016 dose by the end of week 8

For the purposes of this analysis, patients will be considered to have achieved a stable dose of RLY5016 by week 8 if they were dispensed the same dose at the week 6, week 7, and week 8 visits. We will perform these analyses using the methodology described in section 7.2.2.

7.2.7. Time to first serum $K^+$ in the range of 4.0 – 5.0 mEq/L

We will use survival analysis (time to event) methods to describe the time until a patient first reaches serum $K^+$ between 4.0 and 5.0 mEq/L. Patients whose baseline serum $K^+$ is between 4.0 and 5.0 mEq/L will experience the event on Day 1. Patients who discontinue prior to reaching the range will be censored at the date of discontinuation. Patients who reach their week 8 visit but never achieve a serum potassium value within the range will be censored at the week 8 visit. We will construct Kaplan-Meier curves for each randomized starting dose within each stratum to illustrate the time until achieving the goal. Because not all patients will reach the goal, the mean number of days until first in the range for patients in the study sample could underestimate the mean for patients in the population of interest. We will therefor report median time to first serum $K^+$ between 4.0 and 5.0 mEq/L and its 95% confidence intervals for each dose within stratum. We will report the overall p-value from the log-rank statistic comparing the time until achieving the goal across randomized dose groups within stratum.
Kaplan-Meier plots will indicate censored events with symbols. The number of patients within each treatment group at risk of an event at regular time points will appear at the bottom of these figures.

7.2.8. Time to first RLY5016 titration

For patients who experience dose titration during their TIP, we will calculate the number of study days from randomization until the first dose titration. Patients who do not titrate, or who discontinue prior to titration, will be censored at the date of the last dose of RLY5016 during the TIP. We will perform these analyses using the methodology described in section 7.2.7.

7.2.9. Mean number of RLY5016 titrations

We will include all titrations as recorded by the clinical sites and the IVRS system during the TIP, including those that occurred during unscheduled visits. We will not consider a discontinuation of RLY5016 as a dose titration unless it specifically coincided with a protocol-mandated titration based on serum K⁺.

We will present descriptive summaries within each stratum by randomized starting dose and by cohort. We may also describe the number of dose escalations and the number of dose reductions using the same convention. In addition to tabular presentations, we may use figures to illustrate the frequency of titrations. We will not perform inferential tests on the number of dose titrations during the TIP.

7.2.10. Proportion of patients who maintain serum potassium in the range of 3.5 – 5.5 mEq/L by visit and during the entire TIP

We will perform this analysis using a repeated measures logistic regression model within each stratum including data for all scheduled visits within the TIP. We will use a binomial error distribution and a logit link function. Unless otherwise specified, the model will have the following characteristics:

- The response variable will be whether the patient’s serum K⁺ is in the desired range at the scheduled visit
The repeated post-baseline measurement from each patient will be identified by the patient identifier (USUBJID).

The within-patient correlation will be modeled using a heterogeneous Toeplitz structure or, if such a model does not converge, structures that are progressively more restrictive (see section 7.1.1).

The model will include Cohort as a categorical variable. Cohorts 1 and 2 will be combined for this analysis, because there are only three patients in Cohort 2.

The model will contain the baseline serum potassium value as a continuous variable.

The model will also contain the following fixed-effect covariates considered as categorical variables:

- Randomized starting dose
- Time (Visit)
- Randomized starting dose-by-visit interaction.

Because time will be included in the model as a categorical variable, no restriction is imposed on the trajectory of the proportion of patients with serum K\(^+\) in the desired range over time.

We will estimate the proportion of patients with serum K\(^+\) in the desired range for each starting dose and its 95% confidence interval at each scheduled visit and overall.

7.2.11. Proportion of patients who maintain serum potassium in the range of 4.0 – 5.0 mEq/L by visit and during the entire TIP

We will perform these analyses using the methodology described in section 7.2.10.

7.2.12. Proportion of patients who discontinue from the study due to high serum potassium withdrawal criteria

For the purposes of this analysis patients will be considered to have discontinued because of high serum potassium withdrawal criteria if they discontinued, and they had a local laboratory serum potassium value that met criteria for withdrawal for hyperkalemia (see
section 10.2) proximal to the time of discontinuation. We will perform these analyses using the methodology described in section 7.2.2.

7.2.13. Mean change in blood pressure from R0 to weeks 4 and 8

The goal of this analysis is to evaluate the association of blood pressure in the TIP to intervention in the run-in period. We will perform this analysis using an MMRM within each stratum, similar to section 7.1.1. Unless otherwise specified, the MMRM will have the following characteristics:

- The response variable will be the patient’s change in blood pressure from the R0 visit to the date of each measurement
- The repeated measurement from each patient will be identified by the patient identifier (USUBJID)
- The within-patient correlation will be modeled using a heterogeneous Toeplitz structure or, if such a model does not converge, structures that are progressively more restrictive (see section 7.1.1).
- The model will include Cohort as a categorical variable. Cohorts 1 and 2 will be combined for this analysis, because there are only three patients in Cohort 2.
- The model will contain the following fixed-effect covariates considered as categorical variables:
  - Randomized starting dose
  - Time (Visit), taking values T0 (treatment baseline), T5 (week 4), T9 (week 8)
  - Randomized starting dose-by-visit interaction
  - Cohort-by-visit interaction
- The model will contain the following fixed-effect covariates considered as continuous variables:
  - R0 blood pressure value
  - Days since the R0 visit
Inclusion of days since the R0 visit as a continuous covariate adjusts for the effect of variation in time spent in the run-in period across patients when estimating change in blood pressure at the visits of interest (treatment baseline, week 4 visit, and week 8 visit).

We will estimate the mean effect for each starting dose and each cohort and its 95% confidence interval at each visit using linear contrast statements.

7.2.14. Change in UACR from R0 to weeks 4 and 8

For each visit, we will compute the value of UACR as the mean of three measurements if three measurements were obtained; the mean of two measurements if two measurements were obtained; or the value of a single measurement if only one measurement was obtained. We will perform these analyses using the methodology described in section 7.2.13.

7.2.15. Proportion of patients with ≥ 35% reduction in UACR from R0 to week 4 and week 8

For the purposes of this analysis, patients will be considered to have reduced their UACR by at least 35% from R0 to week 8 if the week 8 value of UACR is < 65% of the R0 value of UACR, for UACR computed as in section 7.2.14; and similarly for scheduled visits between R0 and week 8.

We will perform this analysis using a repeated measures logistic regression model within each stratum including data for all scheduled visits from both the run-in phase and the TIP, similar to section 7.2.10. We will use a binomial error distribution with a logit link function. Unless otherwise specified, the model will have the following characteristics:

- The response variable will be whether the patient reduced his or her UACR by at least 35% compared with the R0 visit
- The repeated measurement from each patient will be identified by the patient identifier (USUBJID)
The within-patient correlation will be modeled using a heterogeneous Toeplitz structure or, if such a model does not converge, structures that are progressively more restrictive (see section 7.1.1).

The model will include Cohort as a categorical variable. Cohorts 1 and 2 will be combined for this analysis, because there are only three patients in Cohort 2.

The model will contain the following fixed-effect covariates considered as categorical variables:

- Randomized starting dose
- Time (Visit), taking values T0 (treatment baseline), T5 (week 4), T9 (week 8)
- Randomized starting dose-by-visit interaction
- Cohort-by-visit interaction

The model will contain the following fixed-effect covariates considered as continuous variables:

- R0 blood pressure value
- Days since the R0 visit

Inclusion of days since the R0 visit as a continuous covariate adjusts for the effect of variation in time spent in the run-in period across patients when predicting whether the patient’s UACR was reduced by the desired amount at the visits of interest (treatment baseline, week 4 visit, and week 8 visit).

We will estimate the proportion of patients who reduced their UACR by at least 35% from R0 to each visit of interest for each starting dose and each cohort and its 95% confidence intervals.

7.2.16. Proportion of patients with UACR $\geq 500$ mg/g at baseline (R0) who achieve ACR < 500 mg/g at week 4 and week 8

We will perform these analyses using the methodology described in section 7.2.15.
7.2.17. Proportion of patients with UACR ≥ 300 mg/g at baseline (R0) who achieve ACR < 300 mg/g at week 4 and week 8

We will use these analyses using the same methodology as described in section 7.2.15.

7.2.18. Change in biomarkers from R0 to T0, weeks 4 and 8

Continuous biomarker data will be summarized using the methodology outlined for the primary analysis in section 7.2.3.

7.3. Additional pre-specified outcomes

Pre-specified outcomes listed in section 3.7.5 for the TIP, some of which also involve the run-in period, will be analyzed similar to the analyses presented in sections 7.1 and 7.2. Analyses that include only measures during the run-in phase will include all Cohorts 1 and 2 patients in the RSAF population. These analyses will be descriptive and exploratory; we will make no statistical inference.

7.4. Efficacy exploratory analyses

To examine the effects of the treatment on serum potassium across all patients, we will perform subgroup analyses of the primary outcome on the following groups of patients at baseline:

- Cohorts (non-hyperkalemic [1 and 2] versus hyperkalemic [3])
- Age (65 years or older versus younger than 65)
- Sex (female versus male)
- CKD stage at baseline (4/5 [eGFR <30 mL/min/1.73 m²] versus stages 3 and below [eGFR ≥30 mL/min/1.73m²])
- Heart failure (yes versus no)
- Maximal dose of RAAS inhibitors (maximal dose versus sub-maximal dose)

For each subgroup, we will construct a parallel lines ANCOVA model for the change in central lab serum potassium from baseline until the first dose titration or the week 4 visit, whichever comes first. The model will include randomized starting dose, baseline serum
potassium, subgroup, and an interaction term for subgroup by randomized starting dose. We will report the least squares mean estimate and 95% confidence interval for each combination of subgroup and randomized starting dose using a forest plot.

7.5. **Sensitivity analyses: central and local laboratory values**

Because of the distance between the local sites and the central laboratory, the study may have missing central laboratory data with more complete local laboratory data. We will report the frequency by randomized starting dose and visit of laboratory draws where the clinical site has reported a local serum potassium value but the central laboratory result is not available. As a sensitivity analysis, we will perform the primary and select secondary analyses of serum potassium using local lab values reported on the CRF.

7.6. **Interim analysis**

An interim data analysis was performed for this study when approximately 120 patients (20 patients per group) completed week 4 treatment visit or prematurely terminated the study, prior to SCI’s involvement. Relypsa used these results to select the dose for the Phase 3 study. This SAP includes slight modifications to the previous SAP dated July 2011; these changes are mainly expansions on the definitions and descriptions of the analyses. One notable distinction is the explicit inclusion of cohort as a covariate in the ANCOVA models since randomization was stratified by cohort.

7.7. **Multiplicity**

The primary and secondary objectives of the TIP include dose discovery, efficacy, and safety determination of RLY5016. We will not adjust p-values for the multiple analyses performed for the treatment initiation and long-term maintenance periods. Based on the number of tests included in the analyses of serum potassium, we will report only the nominal p-values.
8. **Safety summaries**

8.1. **Adverse events**

Adverse events (AEs) will be coded by MedDRA 12.0 and summarized by system organ class (SOC) and preferred term (PT). Adverse events will be summarized by patient and where possible by event. We will summarize the events by randomized starting dose; select presentations will also summarize events by treatment dose at onset. Presentations will include all adverse events through seven days after a patient discontinues from the study. No p-values will be computed to test the difference between groups.

Investigators assess the severity (mild, moderate, or severe) and the relationship of each adverse event to study drug. The relationship of each adverse event to RLY5016 will be categorized as not related or related. Because the trial is open-label, we expect differential reporting of “relatedness” by dose of RLY5016 with difficulty in judging whether an event is related to RLY5016. Consequently, most safety analyses will focus on the overall frequency of events by treatment group.

AE presentations for the TIP will summarize events with onset on or after randomization or onset prior to randomization but with worsened severity post-randomization. AEs without a severity rating that are reported post-randomization will be considered treatment-emergent.

Serious adverse events (SAEs) are defined as adverse events that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, are congenital anomalies/birth defects in the offspring of patients taking the study drug, result in persistent or significant disability, or are important medical events. Important medical events are defined as events that may jeopardize the patient or result in medical or surgical intervention to prevent one of the outcomes listed above.

The following presentations of treatment-emergent adverse events for the TIP will be generated:

- Serious adverse events
- All adverse events
• Adverse events of special interest:
  • Cardiovascular adverse events
  • Renal adverse events
• Adverse events related to RLY5016, and
• Adverse events leading to study discontinuation.

Separate summaries of adverse events, such as Data Mosaics© and AETime© figures, may be generated to present the time course and recurrence of events.

All adverse events will be listed with MedDRA 12.0 coding; onset and resolution dates; seriousness; severity; relationship to RLY5016, losaratan, and spironolactone; actions; and outcome.

We will present a separate listing of adverse events that occur during the run-in period. These listings will include events that occurred with onset on or after the first day of the run-in period (R0) up to and including the date of randomization. They will include MedDRA 12.0 coding of the event, seriousness, severity, action, outcome, name and dose of RAAS inhibitor, and dates of onset and resolution with respect to the start of the run-in period.

8.2. Deaths

We will report all deaths among patients who participated in the run-in or who were randomized. The listing will include the date and cause of death, randomized starting dose, stratum, cohort, select co-morbidities at baseline, date of discontinuation of RLY5016 or the dose at onset, and the investigator’s assessment of relationship to study treatment where available.

8.3. Vital signs

Body weight, BMI, blood pressure, and heart rate are collected at each weekly scheduled visit. These data will be summarized for all randomized patients who received at least one dose of RLY5016 by randomized starting dose, and actual dose, by cohort, and by strata at
baseline and follow-up visits. Figures, such as box plots or line graphs, rather than tabular presentation may be used if appropriate.

We will provide separate presentations of vital signs for patients during the run-in period.

8.4  Physical examination

Physical examinations are planned at screening, baseline, and the week 8 visit.

During the study, the number and percentage of patients with each result (change or no change from the last examination) will be summarized. If more than one physical examination is performed for a patient at the same visit, the latest examination will be used. Early withdrawal examinations will be assigned to the closest visit at which an examination was scheduled to occur. The denominators will only include patients with a study visit being summarized.

Results of all physical examinations will be listed.

8.5  Laboratory data

Actual values and change from baseline values for continuous data from laboratory determinations will be summarized descriptively by actual study drug at all scheduled TIP study visits (day 3 and weeks 1 through 8). Categorical data from clinical laboratory tests will be summarized in a similar manner for the actual values.

Exhibit 1 displays the timing of scheduled laboratory tests. Unless otherwise specified, laboratory data will be analyzed using the treatment labels as indicated by the sites. Laboratory data may be analyzed using summary statistics on changes from baseline or distributions or actual values. Figures, such as box plots or Data Mosaics©, rather than tabular presentations may be used if appropriate.

8.5.1  Serum Magnesium Test Results

Clinics collect serum magnesium at the regularly scheduled visits. We will include all records regardless of visit label. We will report the number and percentage of patients
whose magnesium test results are less than 1.8 mg/dL and also less than 1.2 mg/dL during the TIP by randomized study dose within stratum and by cohort. We will present the time-course of serum magnesium below the threshold by regularly scheduled visit and actual study dose using Data Mosaics©. For patients with hypomagnesia, we will generate a listing describing supplemental magnesium use as well as cardiac adverse events.

8.5.2. Proportion of patients who discontinue from the study due to low serum potassium withdrawal criteria

For the purposes of this safety analysis patients will be considered to have discontinued because of low serum potassium withdrawal criteria if they discontinued, and they had a local laboratory serum potassium value that met criteria for withdrawal for hypokalemia (see section 10.2) proximal to the time of discontinuation. We will perform this analysis using the methodology described in section 7.2.2.

8.5.3. Hemoglobin A1c Test Results

Hemoglobin A1c is reported at screening and the week 8 visit. We will use shift tables to descriptively summarize the baseline and change values by randomized starting dose within stratum and cohort.

8.5.4. Serum Fluoride Test Results

Serum fluoride is measured at the central laboratory at baseline, week 4, and week 8. We will use shift tables to descriptively summarize the baseline and change values by randomized starting dose within stratum and cohort. For patients with high serum fluoride (to be defined retrospectively), we will generate listings of gastrointestinal, neurologic, and cardiac adverse events.

8.5.5. Worsening renal failure

The proportion of subjects with worsening renal failure at any time in the run-in period and at any time during the TIP will be calculated. Worsening renal failure will be defined as a ≥100% increase in serum creatinine or a >50% decrease in eGFR from the reference point...
for each time period. The reference point for the run-in period will be R0; T0 will be the reference point for the TIP.

8.6. **Electrocardiogram Findings**

The clinics measure ECGs weekly throughout the TIP. We will summarize continuous measures by visit to demonstrate the change and distribution by visit and randomized starting dose within stratum. We will summarize categorical variables using numbers and percentages, also by visit and randomized starting dose within stratum. Data Mosaics© may also be used to present the time course of select ECG threshold events against treatment of RLY5016.

8.7. **Concomitant medications**

Concomitant medications used during the study will be summarized by cohort and randomized starting dose within stratum. Medications discontinued before the randomization date will be excluded from the summary. The World Health Organization (WHO) Drug Dictionary December 2010 is used to map the medication name to the Anatomical Therapeutic Chemical (ATC) classification codes for summary purpose.

The concomitant medications are classified by the medication category, class, and subgroup based on the ATC-codes. The category is described by the first character of the ATC-code, medication class by the first three characters, and subgroups by all the characters. In general we will report medication class; select medications of specific interest to the study population (such as anti-hypertensives) will be described by subgroup.

We may also provide graphical presentations of use of these concomitant medications with respect to titration of RLY5016.
9. References


10. Appendices

10.1. Appendix 1: Imputation rules

The following are general considerations for missing dates as entered by clinical sites.

10.1.1. Adverse Event

- If onset date is completely missing, the onset date is set to date of first dose.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
  - If year = year of first dose, then set month and day to month and day of first dose
  - If year < year of first dose, then set month and day to December 31st.
  - If year > year of first dose, then set month and day to January 1st.
- If month and year are present and day is missing:
  - If year = year of first dose and month = month of first dose then set day to day of first dose date
  - If month < month of first dose then set day to last day of month
  - If month > month of first dose then set day to first day of month
  - If year < year of first dose then set day to last day of month
  - If year > year of first dose then set day to first day of month
  - For all other cases, set onset date to date of first dose.

10.1.2. Concomitant Medications

- If start date is completely missing, start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
- If year and month are present and day is missing, set day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.
• If year and month are present and day is missing, set day to last day of the month.

10.1.3. Other dates

• If date is completely missing, date will not be imputed.
• If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
• If year and month are present and day is missing, set day to 1st day of month.
10.2. Appendix 2. Treatment initiation titration flowcharts

Exhibit 4. RLY5016 Treatment initiation titration flowchart (visits T0-T1), protocol Appendix C

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1 Decrease RLY5016 dose to 0 g/d only if the patient is currently on 10 g/d
Exhibit 5. RLY5016 Treatment initiation titration flowchart (visits T2-T8), protocol Appendix D

Visits: T2 (Day 8), T3 (Day 15), T4 (Day 22), T5 (Day 29), T6 (Day 36), T7 (Day 43), and T8 (Day 50):
Local Lab Serum K⁺ Value (mEq/L):

<table>
<thead>
<tr>
<th>&lt; 3.5 ¹</th>
<th>3.5—&lt;4.0</th>
<th>4.0—5.0</th>
<th>&gt; 5.0—5.5</th>
<th>&gt; 5.5—&lt;6.2</th>
<th>≥ 6.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Is Current RLY5016 Dose 0 g/d?
  - Yes: RLY5016 Dose ↓ by 10 g/d
  - No: ET Visit (Appendix F)

- Did Serum K⁺ ↓ ≥ 0.4?²
  - Yes: ET Visit (Appendix F)
  - No: RLY5016 Dose Unchanged

- Did Serum K⁺ ↓ ≥ 0.4?²
  - Yes: ET Visit (Appendix F)
  - No: RLY5016 Dose ↑ by 10 g/d

- Same Day Repeat Serum K⁺
  - < 6.2: ET Visit (Appendix F)
  - ≥ 6.2: Titrated RLY5016 per serum potassium criteria above.

- Is Current RLY5016 Dose 60 g/d?
  - Yes: ET Visit (Appendix F)
  - No: RLY5016 Dose ↓ to 10 g/d or to 0 g/d²

- RLY5016 Dose Unchanged
  - Yes: ET Visit (Appendix F)
  - No: Next Scheduled Study Visit

- Mandatory Safety Visit (1, 2, or 3 Days Later)
  - Did Serum K⁺ ↓ ≥ 0.4?²
    - Yes: ET Visit (Appendix F)
    - No: Next Scheduled Study Visit

¹ If serum K⁺ remains < 3.5 mEq/L for 2 consecutive scheduled visits (one week apart) regardless of RLY5016 dose, patient must be withdrawn from the study.
² Compared to the serum potassium value at the previous scheduled visit 1 week ago.
³ Decrease RLY5016 dose to 0 g/d only if the patient is currently on 10 g/d.
Exhibit 6. RLY5016 Treatment initiation titration flowchart (visit M11/Early termination visit), protocol Appendix F

<table>
<thead>
<tr>
<th>M11/Early Termination Visit</th>
<th>Local Lab Serum K⁺ Value (mEq/L):</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ 5.0</td>
<td>&gt; 5.0</td>
</tr>
</tbody>
</table>

- Discontinue RLY5016 at this visit but continue all RAAS inhibitors for 28 days
- Discontinue RLY5016 and all RAAS inhibitors at this visit

Follow-up Visits F1, F2, F3, F4 & F5 3, 7, 14, 21 & 28 Days post-M11/ET, respectively

Follow-up Visits F1 & F2 3 & 7 Days post-M11/ET, respectively

Telephone Calls every 3 months from the last study visit for up to 1 year after T0 Visit

Telephone Calls every 3 months from the last study visit for up to 1 year after T0 Visit
### 10.3. Appendix 3. Schedule of assessments

#### Exhibit 7. Schedule of assessments for long-term maintenance and follow-up

<table>
<thead>
<tr>
<th>Study activity</th>
<th>Study Period</th>
<th>long-term maintenance</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit</td>
<td>M1&lt;sup&gt;B&lt;/sup&gt;</td>
<td>M2&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Week</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Window</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
</tr>
<tr>
<td>Physical Examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Heart Rate and Blood Pressure</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Serum Chemistry</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Hematology (CBC)</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Urine ACR</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Serum Pregnancy Test</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

C = Central lab testing.
L&C = Both Local and Central lab testing (samples should be collected at approximately the same time in the morning for the same patient at all Study Visits including Mandatory Safety Visit, Weekly Maintenance Visit and Unscheduled Visit.

(*) = To be done if applicable.

A. At the T9 Visit patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8 and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule.

B. Starting at Visit T9 and until Week 51 Visit, Mandatory Safety Visits may be required 1-3 and 7 days after the weekly/monthly maintenance visit (see protocol section 3.6.2)

C. As applicable

D. If local lab serum K+ is ≤ 5.0 mEq/L at M11/ET, discontinue RLY5016 but continue all RAAS inhibitors and return for F1, F2, F3 and F4 visits. If local lab serum K+ is > 5.0 mEq/L at M11/ET, discontinue RLY5016 and discontinue all RAAS inhibitors and return for F1 and F2 visits.

E. Mandatory 12-lead, resting ECG if this is the last Follow-up Visit

F. Patients who discontinue from the study will be contacted every 3 months starting from the last study visit until one year after the patient’s Baseline T0 Visit.
### Exhibit 7. Schedule of assessments for long-term maintenance and follow-up, continued

<table>
<thead>
<tr>
<th>Study activity</th>
<th>long-term maintenance</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit M1&lt;sup&gt;B&lt;/sup&gt;</td>
<td>M2&lt;sup&gt;B&lt;/sup&gt;</td>
</tr>
<tr>
<td>Study activity</td>
<td>Window</td>
<td>±3</td>
</tr>
<tr>
<td>Serum Fluoride</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>IxRS Entry</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>RLY5016 Dispensing and Titration&lt;sup&gt;C&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Losartan / Spironolactone Dispensing</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Drug Accountability</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Low Potassium Diet Counseling</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>AE Assessment</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Con Med Assessment</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Urine ACR Supplies Dispensing</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

C = Central lab testing.
L&C = Both Local and Central lab testing (samples should be collected at approximately the same time in the morning for the same patient at all Study Visits including Mandatory Safety Visit, Weekly Maintenance Visit and Unscheduled Visit. (∗∗) = To be done if applicable.

A. At the T9 Visit (see Treatment Initiation SOE), patients who have been on the same dose of RLY5016 at the last 3 consecutive weekly visits (T7, T8, and T9) will be considered stable and will start the monthly (4-week interval) visit schedule. Patients who are not stable at the T9 Visit will return for Weekly Maintenance Visits until they achieve stability (3 consecutive weekly visits on the same RLY5016 dose), at which point they will start the monthly visit schedule.

B. Starting at Visit T9 and until Week 51 Visit, Mandatory Safety Visits may be required 1-3 and 7 days after the weekly/monthly maintenance visit (see section 3.6.2)

C. As applicable

D. If local lab serum K+ is ≤ 5.0 mEq/L at M11/ET, discontinue RLY5016 but continue all RAAS inhibitors and return for F1, F2, F3, F4 and F5 visits. If local lab serum K+ is > 5.0 mEq/L at M11/ET, discontinue RLY5016 and discontinue all RAAS inhibitors and return for F1 and F2 visits

E. Mandatory 12-lead, resting ECG if this is the last Follow-up Visit

F. Patients who discontinue from the study will be contacted every 3 months starting from the last study visit until one year after the patient’s Baseline T0 Visit