Macitentan / ACT-064992

Systemic Sclerosis / Digital Ulcers

Protocol AC-055C302

DUAL-2: Digital Ulcers with mAcitentan in systemic sclerososis

Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis.

Authors: Kelly Papadakis, MD; Loïc Perchenet, PhD; Robin Mukherjee, PhD; Sébastien Roux, MD

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Hereinafter called Actelion

Drug name / number
Macitentan / ACT-064992

Indication
Systemic sclerosis / Digital ulcers

Protocol number, acronym, title

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<td>Kelly Papadakis, MD</td>
<td>8/29/2011</td>
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<td>Clinical Project Leader</td>
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<tr>
<td>Trial Statistician</td>
<td>Robin Mukherjee, PhD</td>
<td>26/8/2011</td>
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</table>
INVESTIGATOR SIGNATURE PAGE

Drug name / number

Macitentan / ACT-064992

Indication

Systemic sclerosis / Digital ulcers

Protocol number, acronym, title


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I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. In particular, I will obtain approval by an Ethics Committee or Institutional Review Board (EC/IRB) prior to study start and signed informed consent from all subjects/patients included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities. I will ensure that the study drug(s) supplied by the sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

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<td>Center Principal Investigator</td>
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<th>Description</th>
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<tbody>
<tr>
<td>ABW</td>
<td>Actual body weight</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANA</td>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic therapeutic chemical</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
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<tr>
<td>CRCL</td>
<td>Creatinine clearance</td>
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<tr>
<td>CREST</td>
<td>Calcinosis; Raynaud’s phenomenon; Esophageal dysfunction; Sclerodactyly; Telangiectasia</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CYP3A</td>
<td>Cytochrome P-450 3A</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DU</td>
<td>Digital ulcer</td>
</tr>
<tr>
<td>DUAL</td>
<td>Digital Ulcers with mAcitentan in systemic scLerosis</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>EOS</td>
<td>End of Study</td>
</tr>
<tr>
<td>EOT</td>
<td>End-of-Treatment</td>
</tr>
<tr>
<td>ERA</td>
<td>Endothelin receptor antagonist</td>
</tr>
<tr>
<td>ET-1</td>
<td>Endothelin 1</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>FWER</td>
<td>Familywise-error rate</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GQM</td>
<td>Global Quality Management</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>HAQ-DI</td>
<td>Health-Assessment-Questionnaire-Disability-Index</td>
</tr>
<tr>
<td>HDISS-DU</td>
<td>Hand Disability in Systemic Sclerosis – Digital Ulcers</td>
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<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>IBW</td>
<td>Ideal body weight</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>IUS</td>
<td>Intrauterine system</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenous(ly)</td>
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<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan Meier</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
</tr>
<tr>
<td>MCP</td>
<td>Metacarpophalangeal</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mITT</td>
<td>Modified intent to treat</td>
</tr>
<tr>
<td>MLA</td>
<td>Marked laboratory abnormalities</td>
</tr>
<tr>
<td>MUSIC</td>
<td>Macitentan US e in an Idiopathic pulmonary fibrosis Clinical study</td>
</tr>
<tr>
<td>NB2</td>
<td>Negative-binomial distribution</td>
</tr>
<tr>
<td>N_d</td>
<td>Total number of new DU s observed up to the last assessment</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No-observed-adverse-effect-level</td>
</tr>
<tr>
<td>p.o.</td>
<td>Orally</td>
</tr>
<tr>
<td>PAH</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>PBO</td>
<td>Placebo</td>
</tr>
<tr>
<td>PD</td>
<td>Pharamcodynamics</td>
</tr>
<tr>
<td>PDE5</td>
<td>Phosphodiesterase type 5</td>
</tr>
<tr>
<td>PGA</td>
<td>Patient global assessment</td>
</tr>
<tr>
<td>PI</td>
<td>Package Insert</td>
</tr>
<tr>
<td>PIP</td>
<td>Proximal interphalangeal</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
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</table>
PP Per-protocol set
q.d. once daily
RAPIDS A randomized, double-blind, placebo-controlled, multicenter study to assess the effect of bosentan on healing and prevention of ischemic digital ulcers in patients with systemic sclerosis
RCT Randomized controlled trials
RP Raynaud’s Phenomenon
SAE Serious adverse event
SAP Statistical Analysis Plan
SERAPHIN Study with endothelin receptor antagonist in pulmonary arterial hypertension to improve clinical outcome
SHAQ Scleroderma Health Assessment Questionnaire
SOC System organ class
SOP Standard operating procedure
SSc Systemic sclerosis
SUSAR Suspected unexpected serious adverse reaction
t.i.d. ter in diem / three times a day
Td Treatment day at the last assessment
TEAE Treatment emergent adverse advent
TGFβ Transforming growth factor beta
T_LOCF Time-adjusted last observation carried forward
ULN Upper limit of normal
VAS Visual analog scale
WHO World Health Organization
WLW Wei–Lin–Weissfeld
WPAI-DU Work Productivity and Activity Impairment Questionnaire: Digital Ulcers
# PROTOCOL SYNOPSIS AC-055C302

<table>
<thead>
<tr>
<th>TITLE</th>
<th>Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis.</th>
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<tr>
<td>ACRONYM</td>
<td>DUAL-2: Digital Ulcers with mAcitentan in systemic scLerosis</td>
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</table>
| OBJECTIVES | **Primary objective**  
  - To demonstrate the effect of macitentan on the reduction of the cumulative number of new digital ulcers at Week 16 in patients with systemic sclerosis and ongoing digital ulcer (DU) disease.  
**Other objectives**  
  - To evaluate the efficacy of macitentan on hand functionality and DU burden at Week 16 in systemic sclerosis (SSc) patients with ongoing DU disease.  
  - To evaluate the safety and tolerability of macitentan in SSc patients with ongoing DU disease.  
  - To evaluate the efficacy of macitentan on time to first DU complication during the entire treatment period. |
| DESIGN / PHASE | Prospective, randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase 3 study. |
| STUDY PLANNED DURATION | First patient First visit  4Q11 | Last patient First visit  4Q13 | Last patient Last visit  2Q14 |
| CENTER(S) / COUNTRY(IES) | Approximately 80 centers in 20 countries (planned). |
| PATIENTS / GROUPS | 285 patients in 3 groups  
  95 patients per group  
  Randomization ratio 1:1:1 (macitentan 3mg: macitentan 10mg: placebo)  
  Patient randomization will be stratified according to the number of DUls at baseline (≤ 3 and > 3 DUls). |
| INCLUSION CRITERIA | 1. Signed informed consent prior to any study-mandated procedure.  
  2. Patients ≥18 years of age. |
3. Women of childbearing potential must use two reliable methods of contraception [see protocol Section 3.3.2 for more details].

4. Diagnosis of SSc according to the classification criteria of the American College of Rheumatology (ACR), or having ever met criteria for CREST syndrome (with sclerodactyly and 2 out of the 4 remaining criteria: calcinosis, Raynaud’s phenomenon, esophageal dysfunction, telangiectasia).

5. At least one visible, active ischemic DU at baseline, located at or distal to the proximal interphalangeal joints (PIP) or at the digital tip, and that developed or worsened within 8 weeks prior to screening (meets protocol defined qualifications for active digital ulcer).

6. History of at least one additional active ischemic DU within 6 months, or at least two within 12 months prior to Screening (Visit 1).

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<tr>
<td>1. DUs due to condition other than SSc.</td>
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<tr>
<td>2. Symptomatic pulmonary arterial hypertension (PAH).</td>
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<tr>
<td>3. Body mass index (BMI: kg/m²) &lt; 18.</td>
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<tr>
<td>4. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) &gt; 1.5 times the upper limit of normal (ULN).</td>
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<tr>
<td>5. Hemoglobin &lt; 75% of the lower limit of the normal range.</td>
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<td>6. Systolic blood pressure &lt; 95 mmHg or diastolic blood pressure &lt; 50 mmHg at Screening (Visit 1) and Randomization (Visit 2).</td>
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<tr>
<td>7. Severe malabsorption, defined as greater than 15% unintentional loss of body weight in the last 6 months prior to randomization; any severe organ failure (e.g., lung, kidney), or any life-threatening condition.</td>
</tr>
<tr>
<td>8. Comorbidities, other than SSc, that could seriously affect the assessment of hand function.</td>
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<tr>
<td>9. Females who are pregnant or breastfeeding or plan to do so during the course of this study.</td>
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<tr>
<td>10. Substance or alcohol abuse or dependence, within 12 months prior to Screening (Visit 1) or tobacco use at any level</td>
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<tr>
<td>EXCLUSION CRITERIA (CONT.)</td>
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<tr>
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<tr>
<td>11. Treatment with PDE5 inhibitors (e.g., sildenafil, tadalafil).</td>
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<tr>
<td>12. Patients on statins (e.g., atorvastatin, simvastatin), who have received treatment for less than 3 months prior to Screening (Visit 1) or whose treatment has not been stable during this period.</td>
</tr>
<tr>
<td>13. Patients on vasodilators, such as calcium channel blockers, ACE-inhibitors, nitroglycerin, alpha adrenergic blockers, or angiotensin II receptor antagonists, N-acetylcysteine, antiplatelet aggregation therapy and low molecular weight heparin who have received treatment for less than 2 weeks prior to Screening (Visit 1) or whose treatment has not been stable during this period.</td>
</tr>
<tr>
<td>14. Treatment with prostanoids regardless of the route of administration within 3 months prior to Screening (Visit 1).</td>
</tr>
<tr>
<td>15. Treatment with disease modifying agents such as methotrexate and cyclophosphamide if present for less than 3 months prior to Screening (Visit 1) or whose treatment has not been stable for at least 1 month prior to Screening (Visit 1).</td>
</tr>
<tr>
<td>16. Treatment with oral corticosteroids (&gt; 10 mg/day of prednisone or equivalent).</td>
</tr>
<tr>
<td>17. Treatment with endothelin receptor antagonists (ERAs) within 3 months prior to Screening (Visit 1).</td>
</tr>
<tr>
<td>18. Systemic antibiotics (oral and i.v.) to treat infected DU(s) within 4 weeks prior to Screening (Visit 1).</td>
</tr>
<tr>
<td>19. Use of topical growth factors, hyperbaric oxygen.</td>
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<tr>
<td>20. Local injection of botulinum toxin in an affected finger within 4 weeks prior to Screening (Visit 1).</td>
</tr>
<tr>
<td>21. Surgical sympathectomy of the upper limbs or surgical wound debridement within 1 month prior to Screening (Visit 1).</td>
</tr>
<tr>
<td>22. Treatment with cytochrome P450 3A (CYP3A) inducers, such as rifabutin, rifampin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John’s wort, within 4 weeks prior to Screening (Visit 1).</td>
</tr>
</tbody>
</table>
| EXCLUSION CRITERIA (CONT.) | 23. Known hypersensitivity to drugs of the same class as the study drug, or any of the excipients.  
24. Planned treatment, or treatment with another investigational drug within 4 weeks prior to Screening (Visit 1).  
25. Any condition that prevents compliance with the protocol or adherence to therapy, including inability to speak, read, or understand the local language well enough to complete all study assessments. |
| CONCOMITANT MEDICATIONS | Allowed  
- Treatments for DUs: Vasodilator treatments, including calcium channel blockers, ACE-inhibitors, nitroglycerin, alpha adrenergic blockers, angiotensin II receptor antagonists, N-acetylcysteine, antiplatelet aggregation therapy and low molecular weight heparin as long as the doses have been stable for at least 2 weeks prior to Screening (Visit 1). Similarly, investigators should keep those treatments constant during Period 1 of the study. During Period 2, dose adjustments of these treatments, while discouraged, may be justified for the treatment of Raynaud’s phenomenon.  
- Analgesics.  
- Topical treatments of DUs (except for growth factors, hyperbaric oxygen).  
- Statins, such as atorvastatin, simvastatin, if present for at least 3 months prior to Screening (Visit 1) at a stable dose and should remain unchanged during the study.  
- Disease modifying treatments such as methotrexate and cyclophosphamide if present for at least 3 months prior to Screening (Visit 1) and at a stable dose for at least 1 month prior to Screening (Visit 1) and remain unchanged during the study.  
- Systemic antibiotics (oral or i.v.). Initiation of systemic antibiotics for the treatment of infection attributed to digital ulceration, is captured under DU complication [Section 3.10.1.9].  
Prohibited  
- Prostanoid treatment, regardless of the route of administration. |
| CONCOMITANT MEDICATIONS (CONT.) | • Treatment with oral corticosteroids (> 10 mg/day of prednisone or equivalent).
|                               | • Local injection of botulinum toxin in an affected finger.
|                               | • Topical growth factors, hyperbaric oxygen.
|                               | • Treatment with PDE5 inhibitors (e.g., sildenafil, tadalafil) is prohibited during Period 1. During Period 2, agents of this class may only be used for intermittent treatment of male erectile dysfunction.
|                               | • CYP3A4 inducers (e.g., rifabutin, rifampin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John’s wort).
|                               | • Endothelin receptor antagonists (e.g., bosentan, ambrisentan).
|                               | • Any investigational drug other than the study drug.

| STUDY PERIODS | Screening period: Up to 2 weeks prior to Baseline/randomization visit.
|              | • The screening period ends with the Baseline visit (Visit 2) at which randomization will take place.
|              | • Period 1: From Baseline (Visit 2) to Week 16. Patients will be randomized to one of three treatment groups (1:1:1): Macitentan 10 mg, macitentan 3 mg, or placebo (PBO).

Patients who prematurely and permanently discontinue study drug during Period 1 must have an End-of-Period 1 visit (Visit 6) at the time of premature discontinuation of study drug.

Upon completion of Period 1, all patients will enter Period 2 and continue on their original assigned treatment, until End-of-Treatment (EOT), which will occur when the last randomized patient not prematurely withdrawn has completed Period 1.

• Period 2: From Week 16 to End-of-Study (EOS) visit.

The EOS will occur when the last randomized patient, not prematurely withdrawn, and who has completed Period 1, completes the 30-day post treatment follow-up visit.

Patients who prematurely and permanently discontinue study drug during Period 2 must have an EOT visit at the time of premature discontinuation of study drug.
| STUDY PERIODS (CONT.) | All patients, whether or not they have prematurely discontinued, will undergo a post-treatment safety follow-up 30 days after discontinuation of study drug. All patients who prematurely and permanently discontinue study drug either during Period 1 or Period 2 (except those who have withdrawn their consent, or are lost to follow-up) will be followed until EOS according to the visit and assessment schedule. **Study Extension:**  
- When the results of the AC-055C301 study become available and a statistically significant favorable effect on ischemic DU with macitentan is demonstrated, an open-label study (under a separate protocol) may be offered to patients who complete the study as scheduled. |
| INVESTIGATIONAL DRUG | Macitentan tablet, doses of 3 mg and 10 mg, once daily. |
| COMPARATIVE DRUG | Matching placebo, once daily. |
| EFFICACY ENDPOINTS | **Primary endpoint (assessed during Period 1)**  
Cumulative number of new DUs up to Week 16. **Other efficacy endpoints**  
Several additional endpoints are listed below that serve as supportive to the primary analysis, and also provide a means of evaluating consistency of results in this study.  
- **Hand Functionality:**  
  i. HDISS-DU  
  ii. HAQ-DI  
- **DU Burden:**  
  i. Binary response of patients without a new DU  
  ii. Binary response of patients with more than 1, 2, 3, etc., new DU(s)  
  iii. Total number of DUs observed  
  iv. Time to onset of each new DU (1st, 2nd, 3rd, 4th, etc., DU) |
| EFFICACY ENDPOINTS (CONT.) | • DU Complications: An event of DU complications is defined as the composite of the following:
  i. Critical ischemic crisis necessitating patient hospitalization.
  ii. Gangrene, (auto)amputation.
  iii. Failure of conservative management: Surgical and chemical sympathectomy, vascular reconstructions, or any unplanned surgery in the management of hand manifestation(s).
  iv. Use of parenteral prostanoids.
  v. Use of endothelin receptor antagonists.
  vi. Requiring class II, III or IV narcotics or increase in existing dose of > 50% as compared to baseline.
  vii. Initiation of systemic antibiotics for the treatment of infection attributed to digital ulceration.
    • Patient-reported global assessment of digital ulcer activity (7 point Likert scale).
    • Physician-reported global assessment of digital ulcer activity (7 point Likert scale).
    • Overall hand pain related to DU(s).
    • Scleroderma Health Assessment Questionnaire (SHAQ).
    • Work Productivity and Activity Impairment Questionnaire: Digital Ulcer (WPAI:DU).
    • Binary response of patients with complete healing of all DU(s).
    • Time to complete healing: This is a time-to-event endpoint. Specifically, it is the time it takes for a patient to achieve complete healing of all DUs. |
| --- | --- |
| TOLERABILITY / SAFETY ENDPOINTS | • Treatment-emergent adverse events (AEs) up to 30 days after last study drug administration.
 • Treatment-emergent serious adverse events (SAEs) up to 30 days after last study drug administration.
 • AEs leading to premature discontinuation of study drug. |
<table>
<thead>
<tr>
<th>TOLERABILITY / SAFETY ENDPOINTS (CONT.)</th>
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</thead>
<tbody>
<tr>
<td>• Treatment-emergent marked laboratory abnormalities (MLAs)*.</td>
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<tr>
<td>• Treatment-emergent electrocardiogram (ECG) abnormalities*.</td>
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<tr>
<td>• Change from baseline in vital signs (blood pressure and heart rate)*.</td>
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<tr>
<td>• Occurrence of liver function test (ALT and/or AST) abnormality (&gt; 3 and ≤ 5 × ULN; &gt; 5 and ≤ 8 × ULN; &gt; 8 × ULN) up to 30 days after last study drug administration.</td>
<td></td>
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<tr>
<td>* up to 24 hours after last study drug administration</td>
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</table>

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<tr>
<th>STATISTICAL METHODOLOGY</th>
<th></th>
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<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Cumulative number of new DUs up to Week 16.</td>
</tr>
<tr>
<td><strong>Null and alternative hypotheses</strong></td>
<td>The global null hypothesis is expressed as a family of two null hypotheses corresponding to the difference of the high-dose and of the low-dose, respectively, versus placebo on the primary endpoint.</td>
</tr>
<tr>
<td><strong>Type-I and -II errors - Power</strong></td>
<td>The overall familywise-error rate (FWER) for multiple comparisons will be controlled by using a closed testing procedure, as specified in Dunnett (1955). The global type II error is set equal to 10%.</td>
</tr>
<tr>
<td><strong>Statistical methodology</strong></td>
<td>The primary analysis will be based on a negative-binomial regression model with stratification factor (≤ 3 and &gt; 3 DUs). The specific methodology of the implementation of the Dunnett’s procedure through the model-based approach will be detailed later, and in the SAP.</td>
</tr>
<tr>
<td><strong>Sample size calculation</strong></td>
<td>A reduction of 45% from the expected 4.4 new ulcers per patient in the placebo group (extrapolated from the RAPIDS-2 study) to 2.4 new ulcers per patient in the bosentan group is considered to be clinically relevant.</td>
</tr>
<tr>
<td></td>
<td>Hence, under the following assumptions:</td>
</tr>
<tr>
<td></td>
<td>• negative-binomial distribution (NB2)</td>
</tr>
</tbody>
</table>
| STATISTICAL METHODOLOGY (CONT.) | • mean number of new DUs on placebo of 4.4  
| | • mean number of new DUs on macitentan (high-dose) 2.4  
| | • overdispersion parameter of 0.76 (based on the RAPIDS studies)  
| | • 10,000 simulation runs,  
| | 95 patients per group provide a power of \( \sim 97\% \) for the comparison of high-dose versus placebo when using the NB2 model. Note: Power for performing the model-independent Pitman’s permutation test, with the above sample size, is 90%.  
| **Main analysis** | The main analysis on the primary efficacy endpoint will be carried out on the mITT set using a NB2 model, with DU3 as a covariate, for the comparison of each active dose versus placebo. Both crude and model-based means differences, and corresponding 95% CIs, on the number of new DUs will be presented. Percent reduction in the mean number of new DUs will also be presented.  
| **Other Efficacy Endpoints** | Other efficacy endpoints will be analyzed with the caveat that any statistical inference will not have any confirmatory value, since no hypothesis was predefined nor sample size estimation performed.  
| **Safety endpoints** | Safety analyses will be carried out descriptively on the Safety set, consisting of all patients who received at least one dose of study drug. The follow-up period will be evaluated considering safety occurrences from the day of the end of study treatment until 30 days thereafter, regardless of the time of study treatment discontinuation.  
| STUDY COMMITTEES | A Steering Committee is involved in the study design and will provide guidance on the study conduct and study publications.  
| | An independent Data Monitoring Committee (DMC) will have access to unblinded safety and tolerability clinical data at regular intervals to monitor patient safety. |
## Table 1  
Visit and assessment schedule

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>Name</th>
<th>SCREENING</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td>Duration</td>
<td>Variable</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 weeks</td>
<td>16 weeks</td>
<td>30 days</td>
</tr>
<tr>
<td>VISITS</td>
<td>Number</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Name</td>
<td>Screening</td>
<td>Randomization</td>
<td>End-of-Period 1</td>
<td>Visits every 3 months</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Visits every month</td>
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<td></td>
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<td></td>
<td>[≥1: ≥17 days]</td>
<td>Visits every month</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>Day -14 to</td>
<td>Day 1</td>
<td>Wk 4</td>
<td>Wk 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤2 weeks</td>
<td></td>
<td>[≥1: ≥17 days]</td>
<td>[≥1: ≥17 days]</td>
</tr>
</tbody>
</table>

1. In the event of treatment discontinuation during the Period 1 prior to Week 16 (whatever the reason), all assessments planned at Visit 6 (End-of-Period 1) must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug.

2. In the event of treatment discontinuation during the Period 2 (whatever the reason), all assessments planned at EOT must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug. The EOT for all ongoing patients will occur when the last randomized patient, not prematurely withdrawn, has completed Period 1.

3. Patients who prematurely and permanently discontinue study drug during either Period 1 or Period 2, will complete the Post-Treatment Visit 30 days after study drug discontinuation, and will continue to be followed until EOS. EOS will occur when the last randomized patient, not prematurely withdrawn, who has completed Period 1, completes the 30-day post treatment follow-up visit.

4. Height performed at Visit 1 only.

5. Blood chemistry and hematology, unless otherwise indicated (Hbg: Hemoglobin; LFT: Liver function tests (include liver aminotransferases, alanine and aspartate aminotransferase, alkaline phosphatase, bilirubin direct and indirect)).

6. Data not collected in eCRF.
<table>
<thead>
<tr>
<th>Time</th>
<th>Day 14 to 3 months</th>
<th>Day 1</th>
<th>Wk 4 [≥ 14 days]¹</th>
<th>Wk 8 [≥ 14 days]²</th>
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<th>Post-Treatment Safety follow-up Visit/EOS</th>
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<tr>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td>Monthly (≥ 7 days) and up to at least 30 days after End-of-Treatment</td>
<td>-</td>
</tr>
</tbody>
</table>

³ Women of childbearing potential only. Serum β hCG will be performed unless otherwise indicated.
⁴ A urine pregnancy test should be performed if Visits 1 and 2 were more than 5 days before Visit 2.
⁵ Total number of DU, occurrence of new DU, healing of all DU, baseline DU and new DU, and location of DU will be performed at each visit.
⁶ It is suggested that during a given visit, the HDSS-DU should be performed once any other assessment(s), followed by the SHAQ.
⁷ Performed at the first two quarterly visits only.
⁸ SAE reporting: Between signature of informed consent and before study drug administration SAEs related to study-mandated procedures only, all SAEs thereafter.
⁹ AEs/SAs should be reported up to 30 days after study drug discontinuation
10 Only medications prescribed for DU and systemic sclerosis (including analgesics)
11 The interval between any two successive visits in period 1 is not to exceed 36 days in total
1 BACKGROUND AND RATIONALE

1.1 Ischemic digital ulcers associated with systemic sclerosis

Systemic sclerosis (SSc), a connective tissue disease characterized by cutaneous and visceral fibrosis and vascular disease, is a rare but potentially devastating condition [Abraham 1997, Charles 2006]. Its annual incidence worldwide during the period from 1969 to 2006 ranged from 0.6 to 122 cases/million, and its prevalence ranged from 7 to 489 cases/million [Chifflet 2008]. SSc is classified into two main subgroups: limited cutaneous systemic sclerosis (skin thickening in the distal limbs but sparing the trunk) and diffuse cutaneous SSc (skin thickening in the proximal and distal limbs and trunk) [Ramirez 2004, Proudman 2007]. Initial symptoms associated with limited or diffuse SSc are usually nonspecific, often including Raynaud’s phenomenon (RP), fatigue, musculoskeletal complaints and hand swelling; esophageal dysfunction is also an early symptom of the disease [Abraham 1997, Charles 2006]. Skin thickening, which typically begins as swelling or puffiness of the skin (usually on the fingers and hands), is the most reliable sign for the diagnosis of the condition.

RP is an almost universal manifestation of SSc [Denton 2003]. It is characterized by vasospasm in response to cold or other stimuli, resulting in impaired oxygenation of the distal extremities and, in some patients, the development of digital ulcers (DUs). DUs are a manifestation of the underlying vasculopathy and fibrosis that characterize SSc.

DUs are a major clinical complication of SSc, occurring in about 30% of the patients each year [Denton 2003]. DUs may occur on the fingers or toes and can manifest on the tips, the finger creases, over the extensor surfaces of the joints or in association with calcinosi s [Denton 2003]. DUs cause local pain and functional impairment (e.g., eating and dressing), and have a major negative impact on quality of life [Denton 2003]. Chronic ulcers can become infected [Denton 2003], resulting in gangrene [Ingraham 2006], osteomyelitis [Korn 2004] and amputation. Of the patients with persistent ulcers, 30% develop irreversible tissue loss [Ingraham 2006]. As a consequence of the progressive scarring and tissue loss that follow healing of ulcers, patients may exhibit permanent disability, with associated social and self-image problems [Korn 2004].

The etiology of DUs is multifactorial [Korn 2004]. DUs are associated with vasculopathy of the fingers and toes, in which the intima of vessels can be thickened and the lumen occluded. Ischemia due to vascular disease, repetitive microtrauma, sclerodactyly, dry skin and calcinosis have all been implicated in the pathogenesis of DUs [Korn 2004].

Management of DUs in SSc involves non-pharmacological and pharmacological modalities for treatment and prevention. The aim of the treatment is to reduce the burden of DUs and their impact on quality of life. This is achieved by reducing pain, restoring hand function, improving digital circulation, preventing infection, promoting healing of
established ulcers, inhibiting the formation of new ulcers and/or reducing the need for hospitalization and amputation.

Several pharmacological therapies for the treatment and prevention of DUs are available for clinical use. Most of the regimens in current usage are empirical and not based on randomized controlled trials (RCT). Potential treatment options include vasoactive drugs such as calcium channel blockers, prostacyclin analogs, selective phosphodiesterase inhibitors, statins, anti-platelet therapy and endothelin receptor antagonists (ERA). To date, only the dual ERA, bosentan, has been approved in Europe for reducing the number of new DUs in SSc patients with ongoing digital ulcer disease, based on two RCT (RAPIDS-1 and RAPIDS-2) [Dhillon 2009]. Outside of Europe, no drug has been approved so far for the treatment of DUs in SSc patients.

Calcium channel blockers, such as nifedipine, are in widespread clinical use for RP. Although there are several studies showing improvement of RP, there is little evidence of their effect on DU [Rademaker 1989].

Prostacyclin analogs, in particular iloprost, are frequently used in patients with severe SSC-related digital vasculopathy. Clinical studies have assessed the efficacy of intravenous iloprost in treating either RP or digital cutaneous lesions, including DUs [Becvar 2005, Wigley 1994]. Two RCT indicate that intravenous iloprost are efficacious in healing DUs in patients with SSc. Intravenous prostanooids (in particular iloprost) should be considered in the treatment of active digital ulcers in patients with SSc based on the EULAR recommendations for the treatment of systemic sclerosis [Kowal-Bielecka 2009]. However, the utility of these therapies is limited by the need for intravenous delivery [Kowal-Bielecka 2009, Wigley 1994, Wigley 1992, Yamane 1992].

Selective phosphodiesterase inhibitors, such as sildenafil, have been investigated for use in patients with RP and have shown significant benefit for the frequency, duration and severity of episodes of RP [Fries 2005]. No prospective studies looking specifically at DU endpoints have yet been conducted.

In addition to the above strategies aiming at specific intervention, management of established DU often entails a multidisciplinary approach involving both pharmacological and non-pharmacological interventions. This includes, among others, analgesics for pain relief, such as opioids, systemic and local antibiotics for infection, and topical treatments (moisturizing creams, emulsifying ointments, topical hydrocolloid, occlusive dressings etc.) to maintain skin flexibility, minimize the occurrence of microtraumatic events and any consequences thereof. Non-pharmacological therapies also include avoidance of triggers of RP such as cold exposure, emotional stress, or vasoconstricting drugs [Hummers 2003]. Surgical intervention (radical microarteriolyis, amputation, sympathectomy, wound debridement, removal of calcinotic nodules) is sometimes needed. In regard to healing, there is sparse clinical data demonstrating effects
on healing of DUs. There remains a clear, unmet medical need for a pharmacological therapy that would affect the natural course of DU in SSc, improve tissue integrity and viability and prevent or reduce the development of new digital ulcers.

1.2 Endothelin and systemic sclerosis
The pathogenesis of SSc is not completely understood. Early vascular injury (as manifested by Raynaud’s phenomenon and nail fold capillary abnormalities), oxidative stress, and inflammation leading to tissue remodeling and fibrosis are important processes [Abraham 2007]. While the precise mechanisms underlying vascular injury are not well known, several mediators are overproduced by endothelial cells in SSc patients, including growth factors, cytokines, matrix metalloproteinases and endothelin 1 (ET-1) [Abraham 2007].

ET-1 is secreted by endothelial cells, smooth muscle cells and fibroblasts, and its production is regulated by a number of soluble factors, including transforming growth factor β (TGF-β) [Abraham 2007]. The actions of ET-1 are mediated by its binding to two receptors: endothelin receptor type A and type B (ET\textsubscript{A} and ET\textsubscript{B}). ET\textsubscript{A} is expressed on mesenchymal cells (smooth muscle cells and fibroblasts) and ET\textsubscript{B} is expressed on endothelial cells. In chronic pathological situations, ET\textsubscript{B} receptors are down-regulated on the endothelium and up-regulated on smooth muscle cells and fibroblasts, thus contributing to the detrimental effects of ET-1 [Abraham 2007].

Relevant to SSc, in smooth muscle cells, ET-1 promotes vasoconstriction and proliferation and increases the production of the key profibrotic factors TGF-β and platelet-derived growth factor (PDGF). In fibroblasts and endothelial cells, ET-1 increases extracellular matrix production and adhesion molecule expression. In macrophages ET-1 leads to activation of nuclear factor kappa B (NF-kb), release of free radicals and increased levels of interleukin-8 (IL-8), monocyte chemoattractant protein 1 (MCP-1) and TGF-β [Abraham 2007].

Several reports have shown elevated blood levels of ET-1 in patients with SSc [Abraham 1997, Kuryliszyn-Moskal 2005, Morelli 1995a, Morelli 1995b, Yamane 1992,]. ET-1 is over-produced by fibroblasts from these patients. Increased expression of ET-1 has also been noted in organs affected by SSc, notably blood vessels, lung, kidney and skin, as well as cell-specific patterns of ET-1 receptor expression, with over-expression of ET\textsubscript{B} in the lungs [Abraham 1997]. Serum ET-1 levels have been correlated with markers of endothelial dysfunction, skin fibrosis, duration of disease and lung diffusion capacity for carbon monoxide [Becvar 2005, Vancheeswaran 1994]. In vitro studies have shown that ET-1 induces lung fibroblasts to produce and contract extracellular matrix, and that the ability of TGF-β to induce profibrotic genes depends on ET-1 [Shi-Wen 2004, Shi-Wen 2007a, Shi-Wen 2007b]. In patients with SSc, especially in those with DUs, ET-1 co-segregates as a biomarker of vascular disease severity, much as it does in the pulmonary hypertension population. This prompted the investigation of the dual ERA, bosentan, for
the management of DUs, and subsequently its approval in Europe for reducing the number of new DUs in SSc patients [Dhillon 2009].

Bosentan showed efficacy in two RCT (RAPIDS-1 and RAPIDS-2) [Korn 2004, Matucci-Cerinic 2010] in SSc patients with DU disease, in particular in those with multiple DUs. In RAPIDS-1, conducted in patients with ongoing or recent DU, bosentan significantly reduced the number of new DUs (mean 1.3 [48%] fewer new DUs per patient over 16 weeks; p < 0.05 vs placebo). The efficacy of bosentan was corroborated by the results of RAPIDS-2, which was conducted in SSc patients with active DUs at baseline, a population considered to be at high risk of peripheral digital necrosis, (mean 0.8 [30%] fewer new DUs per patient over 24 weeks; p < 0.05 vs placebo).

Taken together, these data suggest that ET-1 is a mediator that impacts both vascular injury and the fibrotic process in patients with SSc, making blockade of its functions an appealing therapeutic target.

1.3 Macitentan – endothelin receptor antagonist

1.3.1 Macitentan – preclinical information

Macitentan / ACT-064992 is a new, orally active, non-peptide, potent dual \( \text{ET}_A \) and \( \text{ET}_B \) receptor antagonist selected for clinical development in PAH and other indications associated with an activated ET-system. Macitentan shows dose-dependent efficacy in preclinical models of hypertension and pulmonary arterial hypertension (PAH), and is approximately ten times more potent than bosentan based on administered dose.

In preclinical safety studies, no effects on normal physiological functions or electrocardiogram (ECG) variables, including cardiac repolarization, were observed, with the exception of a decrease in arterial blood pressure observed in a cardiovascular study in dogs. Macitentan has no genotoxic potential. In the pivotal 26-week and 39-week toxicity studies (in the rat and dog, respectively), the exposures in animals found at the no-observed-adverse-effect-levels (NOAEL) were above the anticipated clinical exposures and provide a margin of safety for studies in man. A study conducted in hairless rats showed that macitentan is not phototoxic in vivo. Macitentan does not bind relevantly to melanin. Reproductive toxicity studies showed that macitentan is teratogenic without affecting male or female fertility. Teratogenicity is considered to be an ERA class effect.

More detailed information on macitentan can be found in the Investigator’s Brochure [ACT-064992 IB].
1.3.2 Macitentan – clinical information

1.3.2.1 Pharmacology studies

During the Phase 1 program, more than 150 healthy male subjects were treated with macitentan. Macitentan was well tolerated in all studies. The most frequently reported adverse event (AE) was headache. No clear dose relationship could be discerned for any AE. However, in the single-ascending dose study, compared to subjects receiving placebo, subjects receiving a dose of 600 mg reported markedly more AEs (headache, nausea, vomiting, rhinitis, and others). A dose of 300 mg was identified as the maximum tolerated dose.

Treatment with macitentan up to 600 mg as a single dose and 30 mg as multiple doses for 10 days (highest doses tested) was not associated with clinically relevant changes in systolic and diastolic blood pressures, heart rate, or ECG intervals or morphology.

Three cases of asymptomatic increases in liver function tests (LFTs) greater than three times the upper limit of normal (ULN) were observed. The increase in liver aminotransferases was not associated with any AE, and resolved within 14 days of observation.

In healthy male subjects, the plasma concentration-time profile of macitentan can be described by slow absorption with maximum plasma concentrations achieved approximately 8 hours after dosing. The apparent elimination half-life is approximately 16 hours. After multiple dosing, the pharmacokinetics of macitentan are dose-proportional. Steady-state conditions are reached by Day 3 and macitentan accumulates approximately 1.5-fold. In plasma, one pharmacologically active metabolite has been identified, ACT-132577. This metabolite has an apparent elimination half-life of about 2 days. The accumulation factor is approximately 8.5. There are no signs that macitentan induces its own metabolism.

Macitentan increased plasma ET-1 concentrations for all single doses from 5 mg upwards. When given as multiple doses, a dose-dependent increase in plasma ET-1 concentrations was observed with doses from 1 to 10 mg, with no further increase noted at 30 mg.

Results from the food interaction study showed that macitentan can be taken irrespective of food intake.

Macitentan did not influence the pharmacokinetics or pharmacodynamics of warfarin. Co-administration of warfarin with macitentan did not have an impact on the exposure to macitentan.

There were no clinically relevant effects of sildenafil 20 mg t.i.d. on the pharmacokinetics of macitentan and its metabolite (ACT-132577). Also, no effect of
Macitentan was observed on the pharmacokinetics of sildenafil and its metabolite (N-desmethyl sildenafil).

Exposure to macitentan increased by approximately a factor of 2 after concomitant treatment with ketoconazole. ACT-132577 exposure was not influenced by ketoconazole treatment. The magnitude of the interaction is considered not to be clinically relevant and, therefore, macitentan may be concomitantly administered with cytochrome P450 3A4 (CYP3A4) inhibitors.

Three studies have been clinically completed but not yet reported. Study AC-055-110 was performed to assess the effect hepatic impairment due to liver cirrhosis on the pharmacokinetics of macitentan. Preliminary results from this study reveal that no dose adaptation is needed in hepatically impaired subjects. Study AC-055-111 was performed to investigate (mutual) drug-drug interactions with rifampicin and cyclosporine. Preliminary results from this study indicate that there was no pharmacokinetic interaction with cyclosporine while the exposure to macitentan decreased to a clinically relevant extent in the presence of rifampicin. Study AC-055-112 was performed to assess the effect of renal impairment on the pharmacokinetics of macitentan. Preliminary results from this study indicate that compared to healthy subjects, the pharmacokinetics of macitentan and metabolites differed in patients with severe renal function impairment. In the severely renally impaired patients, increases in AUC_{0-\infty} of 27%, 58%, and 646% were observed for macitentan, ACT-132577, and ACT-373898, respectively. However, the increase in exposure to macitentan and the active metabolite in patients with severely impaired renal function are not considered clinically relevant and therefore do not necessitate dose adjustment in this patient population.

More detailed information on macitentan Phase 1 studies can be found in the Investigator’s Brochure [ACT-064992 IB].

### 1.3.2.2 Phase 2 study in patients with essential hypertension

A Phase 2 dose-finding study was conducted over 8 weeks in 379 patients with mild to moderate essential hypertension. Four doses of macitentan (0.3, 1, 3, and 10 mg) and enalapril (20 mg) once daily were evaluated versus placebo. Treatment with macitentan 10 mg showed a statistically significant reduction vs placebo in sitting diastolic and systolic BP at trough, and a dose-response for effect was indicated. Most of the BP reduction with macitentan was reached within 4 weeks of treatment. The pharmacokinetics and pharmacodynamics analysis indicated that the 10 mg dose is close to the plateau of the pharmacological effect.

Macitentan was well tolerated across all four dose levels. The overall frequency of AEs was similar to that observed in the placebo group. During the study, five cases of increased liver enzymes > 3 × ULN were observed. Given this finding, the sponsor did not consider the risk/benefit favorable for this indication and consequently, the study was
prematurely discontinued. These five cases occurred in the macitentan groups, without obvious dose relationship (one, two, one, and one in the 0.3-mg, 1-mg, 3-mg, and 10-mg dose groups, respectively). All episodes of liver enzyme elevations resolved without sequelae within 14 days of observation. However, these data suggest that like other ERAs, macitentan may cause liver aminotransferase elevations in some patients.

More detailed information on macitentan Phase 2 can be found in the Investigator’s Brochure [ACT-064992 IB].

1.3.2.3 Phase 2 study in patients with idiopathic pulmonary fibrosis

A Phase 2 study (MUSIC) is currently ongoing to assess the effects of macitentan on pulmonary function tests in patients with idiopathic pulmonary fibrosis. During this study, an independent Data Monitoring Committee (DMC) reviews unblinded safety and tolerability clinical data at regular intervals to monitor patient safety. In May 2011, 178 patients had been enrolled, with a mean study drug exposure of 14.6 months.

1.3.2.4 Phase 3 study in patients with pulmonary arterial hypertension

A Phase 3 study (SERAPHIN) is currently ongoing to assess the effects of macitentan on morbidity and mortality in patients with symptomatic PAH. During this PAH study, an independent DMC reviews unblinded safety and tolerability clinical data at regular intervals to monitor patient safety. In May 2011, 742 patients had been enrolled, with a mean study drug exposure of 17.7 months.

1.4 Study rationale

1.4.1 Medical and regulatory background

The use of an ERA is an attractive approach in combating the structural vascular damage observed in SSc leading to complications such as PAH and DUs. Tracleer® (bosentan) has been approved in Europe and is indicated to reduce the number of new DUs in patients with SSc and ongoing DU disease. To date, there is a paucity of studies in this indication, with no established precedence other than the experience brought forth in the field from the two RAPIDS studies with bosentan. There are also no regulatory guidelines evaluating the efficacy of medicinal products in this therapeutic area and formal clinical guidelines for the management of DU do not exist.

Macitentan is a potent dual ERA selected for clinical development in DUs associated with SSc and other indications associated with an activated ET-system. This compound has been optimized in preclinical studies for its ability to block the detrimental effects of ET-1.

1.4.2 Patient population

The completed clinical program with bosentan has provided evidence of clinical benefit in digital ulceration associated with SSc by demonstrating that bosentan reduces the
number of new DUs in these patients. The greatest benefit was obtained in patients with most active disease, with reductions in new DU most prominent in patients with high ulcer burden at the start of treatment. Consequently, the study population for this study will be chosen to represent a target population of patients with high propensity for developing new DU, thought to be those with at least an active ischemic DU of recent onset located at or distal to the proximal interphalangeal (PIP) joints, and with at least one additional active ischemic DU during the last 6 months, or a recent history of multiple active ischemic DUs (in the last 12 months prior to enrollment).

1.4.3 Study design
This is a prospective, randomized (1:1:1, macitentan 3 mg: macitentan 10 mg: placebo), double-blind, placebo-controlled, multicenter, parallel group, Phase 3 study.

This study is designed to assess the efficacy and safety of macitentan in patients with digital ulceration associated with SSc. At least 285 patients will be enrolled in 3 groups (95 patients per group). The screening period will be completed in 2 weeks (14 days) maximum per patient.

The double-blind treatment period is of variable duration. It consists of a fixed period from baseline (Visit 2) to the primary endpoint evaluation (Week 16 or earlier in case of premature discontinuation of study medication - Period 1) and a variable period from the primary endpoint evaluation to End-of-Study (EOS) (Period 2). All patients completing Period 1 will continue on their original randomized treatment into Period 2, until End-of-Treatment (EOT) which will occur when the last randomized patient, not prematurely withdrawn, has completed the 16-week Period 1.

All patients will be followed-up until the EOS visit. The EOS visit will occur when the last randomized patient, not prematurely withdrawn, and who has completed Period 1, completes the 30-day post-treatment (safety follow-up) visit.

The primary objective is to demonstrate the effect of macitentan on the reduction of the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcers.

Other objectives of this study include the evaluation of the efficacy of macitentan on hand functionality, DU burden and DU complication(s) in SSc patients with ongoing DU disease , as well as the overall evaluation of the safety and tolerability of macitentan in these patients.

1.4.4 Comparative drug(s) and/or placebo
Several pharmacological therapies for the treatment and prevention of DUs are available for clinical use worldwide. However, to date, only the dual ERA, bosentan, has been approved in Europe for reducing the number of new DUs in SSc patients with ongoing
digital ulcer disease [Dhillon 2009]. Outside of Europe, no drug has been approved so far for the treatment of DUs in SSc patients.

Patients who participate in this study will receive macitentan (3 or 10 mg), or matching placebo in addition to other existing treatments for digital ulceration [Section 3.3.4.1].

1.4.5 Dose selection

The proposed doses (3 and 10 mg once daily) for this study are based mainly on the experience gained from the Phase 1 studies in healthy volunteers (AC-055-101, AC-055-102), and from the Phase 2 study in essential hypertension, AC-055-201 [ACT-064992 IB].

In the multiple ascending dose study, AC-055-102, macitentan induced increased plasma ET-1 levels at all doses tested after 10 days of treatment (1, 3, 10, and 30 mg q.d.). A dose-dependent increase was observed from 1 to 10 mg, with no further increase noted at 30 mg. Therefore, it was concluded that 10 mg q.d. would be the dose that would produce the maximum effect on the endothelin system.

In the Phase 2 dose-ranging study in essential hypertension (AC-055-201), which tested four doses of macitentan (0.3, 1, 3, and 10 mg q.d.), the 3- and 10-mg dose levels were associated with increases in plasma ET-1 levels which were not observed with lower doses (0.3 and 1 mg), suggesting that blockade of ET<sub>B</sub> receptors (and consequently ET<sub>A</sub> receptors as well, given the affinity characteristics of the drug) was effective with 3- and 10-mg doses. This study demonstrated that macitentan is efficacious in reducing the blood pressure of subjects with essential hypertension, with response to macitentan that appeared to be dose-dependent, with the most pronounced BP reduction attained at dose levels above 3 mg, with the 10 mg dose close to the plateau of pharmacological effect. On the basis of these observations, it appears that macitentan doses of 3 mg and 10 mg q.d. are appropriate for further clinical testing aimed to establish the potential of macitentan as a therapeutic approach for the treatment of the vasculopathic manifestations of systemic sclerosis.

1.4.6 Treatment duration

Period 1: The duration of treatment has been set at 16 weeks for study Period 1, to allow a thorough evaluation of the potential of macitentan to reduce the number of new DUs (primary endpoint), and to improve hand functionality and DU burden (other endpoints) during this period. This is considered a reasonable time-span to achieve a reduction in the occurrence of new DUs with macitentan that would also translate into relevant clinical benefit for the patient by ameliorating hand function. In RAPIDS 1, a period of 16 weeks of bosentan treatment was sufficient to observe a clinically meaningful reduction in numbers of new DUs vs placebo. During the 16 weeks of double-blind therapy, patients on bosentan had 48% fewer new DUs than those on placebo (means of 1.4 vs 2.7 new ulcers, respectively).
Period 2: Treatment is extended for a period of variable duration (until EOT, which will occur when the last randomized patient not prematurely withdrawn has completed Period 1), to evaluate over an extended period, the safety, tolerability, and efficacy of macitentan in patients with systemic sclerosis and ongoing digital ulcers.

1.4.7 Primary endpoint
‘Cumulative number of new DUs’ was chosen as the primary endpoint for this study, mainly driven by the previous experience from the RAPIDS studies where a consistent effect of bosentan treatment was observed on the reduction of the number of new digital ulcers (total number of new DU per patient).

The study design for this development program is mainly driven and supported by results from the completed double-blind, placebo-controlled RAPIDS-1 and RAPIDS-2 studies with bosentan [Korn 2004, Matucci-Cerinic 2010], for which input had been received from the regulatory authorities, as well as from the Steering Committee involved in the study design.

1.4.8 Statistical hypotheses and sample size
Details provided in Section 5 (Statistical Methodology and Analyses).

2 STUDY OBJECTIVES

2.1 Primary objective

- To demonstrate the effect of macitentan on the reduction of the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

2.2 Other objectives

- To evaluate the efficacy of macitentan on hand functionality and DU burden at Week 16 in SSc patients with ongoing DU disease.
- To evaluate the safety and tolerability of macitentan in SSc patients with ongoing DU disease.
- To evaluate the efficacy of macitentan on time to first DU complication during the entire treatment period.

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

3.2 Overall study design
This is a prospective, randomized, double-blind, parallel-group, placebo-controlled, multicenter study designed to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis.
The study consists of 3 consecutive periods:

1. **A screening period** of a maximum of 2 weeks before randomization.

2. **Period 1**: Patients will be randomized to one of the three treatments (1:1:1 macitentan 3 mg; macitentan 10 mg; placebo). Patient randomization will be stratified according to the number of DUs at baseline (≤ 3 and > 3 DUs).

   Primary endpoint assessment (cumulative number of new DUs) is planned at the End-of-Period 1 (Week 16).

   If the patient is prematurely and permanently discontinued from study medication during Period 1 prior to Week 16 (whatever the reason), all assessments planned at Week 16 (End-of-Period 1) must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug. Upon completion of Period 1, all patients will enter Period 2 and continue on their original assigned treatment, until EOT, which will occur when the last randomized patient not prematurely withdrawn has completed Period 1.

3. **Period 2**: From Week 16 to EOS visit.

   The EOS will occur when the last randomized patient, not prematurely withdrawn, and who has completed Period 1, completes the 30-day post-treatment follow-up visit.

   If the patient is prematurely and permanently discontinued from study medication during the Period 2, all assessments planned at EOT must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug.

   All patients who prematurely and permanently discontinue study drug either during Period 1 or Period 2 will continue to be followed until EOS according to the visit and assessment schedule.

   All patients, whether or not they have prematurely discontinued, will undergo a post-treatment safety follow-up visit 30 days after discontinuation of study drug.

   A total of approximately 285 patients will be treated in this study. The study will be conducted at approximately 80 centers and in approximately 20 countries.

   The study is foreseen to start in Q4 2011 with the First Patient First Visit and to end in Q2 2014 with the Last Patient Last Visit.

   The Steering Committee was involved in the design of the study and will be consulted for any substantial protocol amendment, if needed.

   No interim analysis for efficacy is planned. During this study, an independent Data Monitoring Committee (DMC) will review unblinded safety and tolerability clinical data
at regular intervals to monitor patient safety. An open-label study extension (under a separate protocol) may be offered to patients who complete the study as scheduled when the results of the AC-055C301 study become available, and a statistically significant favourable effect on ischemic DU with macitentan is demonstrated.

Figure 1  Study design

3.3 Study population
3.3.1 Patient population
The patient population involves SSc patients suffering from ongoing DU disease.

3.3.2 Inclusion criteria
Eligible patients must meet all of the following inclusion criteria during the initial screening visit of the study and prior to first dose of study medication:

1. Signed informed consent prior to any study-mandated procedure.
2. Patient’s ≥ 18 years of age.
3. Women of childbearing potential must use two reliable methods of contraception.

Women of childbearing potential* with a negative serum pre-treatment pregnancy test are allowed in the study if they consistently and correctly use (from screening and up to 30 days after study treatment discontinuation) two reliable methods of contraception at the same time. Reliable methods of contraception include intrauterine devices or intrauterine systems, tubal sterilization, hormonal methods (combined or progesterone only oral contraceptives, transdermal patches, vaginal
rings, injections, implants) and barrier methods (male condom, diaphragm, or cervical cap). A partner’s vasectomy still requires one additional method of contraception. Abstinence, the rhythm method, or contraception by the other partner alone, will not be considered reliable methods of contraception.

*A woman is considered to have childbearing potential unless she meets at least one of the following criteria:

– previous bilateral salpingo-oophorectomy or hysterectomy
– premature ovarian failure confirmed by a specialist gynaecologist
– pre-pubescence, XY genotype, Turner syndrome, uterine agenesis
– age > 50 years and not treated with any kind of hormone replacement therapy (HRT) for at least 2 years prior to screening, with amenorrhea for at least 24 consecutive months prior to screening. An assessment of serum follicle stimulating hormone (FSH) showing a level of > 40 IU/L at screening may be used to exclude childbearing potential, based on the discretion of the investigator.

4. Diagnosis of SSc according to the classification criteria of the American College of Rheumatology (ACR) [Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee 1980], or having ever met criteria for CREST syndrome (with sclerodactyly and 2 out of the 4 remaining criteria: calcinosis, Raynaud’s phenomenon, esophageal dysmotility, and telangiectasia).
<table>
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<th>CRITERION</th>
<th>DESCRIPTION</th>
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<tr>
<td><strong>MAJOR CRITERION</strong></td>
<td>Proximal scleroderma Tightness, thickening, and non-pitting induration changes excluding the localized forms of scleroderma (morpha or linear scleroderma) proximal to the metacarpo-phalangeal or metatarso-phalangeal joints, affecting other parts of the extremities, face, neck or trunk.</td>
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| **MINOR CRITERIA**        | • Sclerodactyly Tightness, thickening, and non-pitting induration limited to fingers and toes.  
• Digital pitting scars of fingertips or loss of substance of the distal finger pad  
• Bibasilar pulmonary fibrosis Depressed areas at tips of digits or loss of digital pad tissue as a result of digital ischemia rather than trauma or exogenous causes.  
Bilateral reticular pattern of linear or lineonodular densities which are most pronounced in basilar portions of the lungs on standard chest roentgenogram. |

The ACR criteria for the classification of SSc require 1 major criterion, or 2 of the 3 minor criteria as per the table above.

Systemic sclerosis is sub-classified as:

Diffuse SSc involving scleroderma skin change in locations proximal to the elbows or knees inclusive of the chest and abdomen (face involvement does not qualify). Individuals with skin thickening proximal to the wrist who are within 6 months of their first non-Raynaud manifestation AND who have palpable tendon friction rubs in at least two locations are also classified as diffuse SSc.

Limited SSc characterized by scleroderma skin change restricted to sites distal to the elbows and knees (face involvement does not disqualify).

- Patients who are not classifiable by the above descriptions cannot be included in the study.

5. At least one visible, active ischemic digital ulcer (DU) at baseline, located at or distal to the PIP joints or at the digital tip, and that developed or worsened within 8 weeks prior to screening. Must meet protocol defined qualifications for active DU:
   - An active DU is defined as a lesion on the finger with visually discernable depth and a loss of continuity of epithelial coverage that is associated with pain not felt to be attributed to other etiologies such as infection, trauma, arthritis etc. This
definition does not include fissures, paronychia, digital pitting scars, extrusion of calcium, and indeterminate lesions (lesions of which denudation is not clearly visible and cannot be judged, because of the presence of a scab or necrotic tissue). Only DUs from the PIP joints distally, including the digital tip will be assessed. Digital ulcers proximal to PIP joints, such as those over the metacarpophalangeal (MCP) joints will not be assessed.

6. History of at least one additional active ischemic DU within 6 months, or at least two within 12 months prior to Screening (Visit 1).

3.3.3 Exclusion criteria

Eligible patients must meet none of the following exclusion criteria:

1. DUs due to condition other than SSc.
2. Symptomatic pulmonary arterial hypertension (PAH).
3. Body mass index (BMI: kg/m²) < 18.
4. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN).
5. Hemoglobin < 75% of the lower limit of the normal range.
6. Systolic blood pressure < 95 mmHg or diastolic blood pressure < 50 mmHg at Screening (Visit 1) and Randomization (Visit 2).
7. Severe malabsorption, defined as greater than 15% unintentional loss of body weight in the last 6 months prior to randomization; any severe organ failure (e.g., lung, kidney), or any life-threatening condition.
8. Comorbidities, other than SSc, that could seriously affect the assessment of hand function.
9. Females who are pregnant or breastfeeding or plan to do so during the course of this study.
10. Substance or alcohol abuse or dependence, within 12 months prior to Screening (Visit 1) or tobacco use at any level within the past 6 months prior to Screening (Visit 1).
11. Treatment with PDE5 inhibitors (e.g., sildenafil, tadalafil).
12. Patients on statins (e.g., atorvastatin, simvastatin), who have received treatment for less than 3 months prior to Screening (Visit 1) or whose treatment has not been stable during this period.
13. Patients on vasodilators, such as calcium channel blockers, ACE-inhibitors, nitroglycerin, alpha adrenergic blockers, or angiotensin II receptor antagonists, N-acetylcysteine, antiplatelet aggregation therapy and low molecular weight heparin
who have received treatment for less than 2 weeks prior to Screening (Visit 1) or whose treatment has not been stable during this period.

14. Treatment with prostanoids regardless of the route of administration within 3 months prior to Screening (Visit 1).

15. Treatment with disease modifying agents such as methotrexate and cyclophosphamide if present for less than 3 months prior to Screening (Visit 1) or whose treatment has not been stable for at least 1 month prior to Screening (Visit 1).

16. Treatment with oral corticosteroids (> 10 mg/day of prednisone or equivalent).

17. Treatment with endothelin receptor antagonists (ERAs) within 3 months prior to Screening (Visit 1).

18. Systemic antibiotics (oral and IV) to treat infected DU(s) within 4 weeks prior to Screening (Visit 1).

19. Use of topical growth factors, hyperbaric oxygen.

20. Local injection of botulinum toxin in an affected finger within 4 weeks prior to Screening (Visit 1).

21. Surgical sympathectomy of the upper limbs or surgical wound debridement within 1 month prior to Screening (Visit 1).

22. Treatment with cytochrome P450 3A (CYP3A) inducers, such as rifabutin, rifampin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John’s wort, within 4 weeks prior to Screening (Visit 1).

23. Known hypersensitivity to drugs of the same class as the study drug, or any of their excipients.

24. Planned treatment, or treatment with another investigational drug within 4 weeks prior to Screening (Visit 1).

25. Any condition that prevents compliance with the protocol or adherence to therapy, including inability to speak, read, or understand the local language well enough to complete all study assessments.

3.3.4 Concomitant medications

3.3.4.1 Allowed concomitant medications

- Patients usual treatments for DUs: Vasodilator treatments, including calcium channel blockers, ACE-inhibitors, nitroglycerin, alpha adrenergic blockers, angiotensin II receptor antagonists, N-acetylcysteine, antiplatelet aggregation therapy and low molecular weight heparin as long as the doses have been stable for at least 2 weeks prior to Screening (Visit 1). Similarly, investigators should keep those treatments constant during Period 1 of the study. During Period 2, dose adjustments of these
treatments, while discouraged, may be justified for the treatment of Raynaud’s phenomenon.

- Analgesics. Analgesics given for DU pain or for any other reason will be recorded in a patient diary, along with dose adjustments during the study.

- Topical treatments of DUs such as antiseptics, antibiotics, nitrate ointment, protective ointments, etc., (except for growth factors, hyperbaric oxygen). Topical treatments will be recorded in the section of concomitant medications of the eCRF.

- Statins, such as atorvastatin, simvastatin, if present for at least 3 months prior to Screening (Visit 1) at a stable dose, and should remain unchanged during the study.

- Disease modifying treatments such as methotrexate and cyclophosphamide if present for at least 3 months prior to Screening (Visit 1) and at a stable dose for at least 1 month prior to Screening (Visit 1) and remain unchanged during the study.

- Systemic antibiotics (oral or IV). Systemic antibiotics for the treatment of DUs 4 weeks prior to screening (Visit 1) are an exclusion criterion in order to exclude patients who already have recalcitrant, chronic, hard-to-heal ulcers not amenable to healing at baseline. However, systemic antibiotics are allowed during the course of the study period. Initiation of systemic antibiotics for the treatment of infection attributed to digital ulceration, is captured under DU complication [section 3.10.1.9].

3.3.4.2 Prohibited concomitant medications

- Prostanoid treatment, regardless of the route of administration (parenteral, inhaled or per os). The use of parenteral prostanoids during the study, if needed, will be recorded as a DU complication [Section 3.10.1.9]. Regarding the other routes of administration, the need to use prostanoids, for example for class II PAH, will lead to permanent discontinuation of the study medication but will not be recorded as a DU complication.

- Oral corticosteroids (> 10 mg/day of prednisone or equivalent).

- Local injection of botulinum toxin in an affected finger.

- Topical growth factors, hyperbaric oxygen.

- Treatment with PDE5 inhibitors (e.g., sildenafil, tadalafil) is prohibited during Period 1. During Period 2, agents of this class may only be used for intermittent treatment of male erectile dysfunction.

- CYP3A4 inducers (e.g., rifabutin, rifampin, rifapentin, carbamazepine, phenobarbital, phenytoin, St. John’s wort).

- Endothelin receptor antagonists (e.g., bosentan, ambrisentan).

- Any investigational drug other than the study drug.
3.4 Study drugs

Study drug includes investigational drug macitentan and matching placebo.

3.4.1 Investigational drug and matching placebo

Treatment with macitentan will be compared to treatment with placebo. In Period 1, patients who have met all inclusion and none of the exclusion criteria, will be randomized (double-blind) in a 1:1:1 manner to receive one of three treatment regimens (3mg, 10 mg or placebo), in addition to their usual treatment for SSC. All patients completing Period 1 will subsequently continue on their original randomized treatment until EOT (as described in Section 3.4.2).

Double-blind study medication will be provided as 3 mg and 10 mg tablets supplied in 60 mL HDPE bottles by Actelion Pharmaceuticals Ltd. Medication labels will comply with the legal requirements of each country. The storage conditions for study medication will be described on the medication label.

The study medication is to be stored at room temperature (below 25 °C/77 °F).

The first intake of study drug will take place at the randomization visit after successful completion of all assessments. Thereafter, one tablet should be administered orally once daily, irrespective of food intake, every morning throughout the study.

Actelion Pharmaceuticals Ltd will supply the following study medications:

- Macitentan: 3 mg and 10 mg tablets
- Matching placebo

Study medication and matching placebo will be supplied in childproof bottles containing 36 tablets. For patients with difficulty opening study medication bottles, pills may be distributed in pill boxes during each site visit. Missed doses of study medication will not be made-up and the patient will resume the regular dosing schedule.

3.4.2 Study drug dosing scheme

Period 1:

Patients who have met all inclusion and none of the exclusion criteria will be randomized (double-blind) in a 1:1:1 manner to receive one of three treatment regimens in addition to their usual treatment for SSC:

- Macitentan 10 mg q.d.
- Macitentan 3 mg q.d.
- Placebo q.d.
Patient randomization will be stratified according to the number of DUs at baseline (≤ 3 and > 3 DUs).

**Period 2:**

Upon completion of Period 1, all patients will enter Period 2 and continue on their original assigned treatment, until EOT, which will occur when the last randomized patient not prematurely withdrawn has completed Period 1.

**3.4.3 Study drug up- and down-titration**

Not applicable.

**3.5 Study drug discontinuation and study withdrawal**

**3.5.1 Study drug interruption or discontinuation**

The investigator must temporarily interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the patient.

- The interruption or premature discontinuation of study drug might be triggered by an adverse event (AE), a diagnostic or therapeutic procedure or initiation of prohibited therapy [Section 3.3.4.2], an abnormal assessment (e.g., ECG or laboratory abnormalities), in case of DU complication [Section 3.10.1.9], or for administrative reasons – in particular withdrawal of the patient’s consent. The reason for study drug interruption or premature discontinuation must be documented in the electronic case report form (eCRF).

**All decisions to discontinue study medication permanently should be discussed, if possible, with a representative of Actelion Pharmaceuticals Ltd.**

If the reason for the interruption or discontinuation of the study drug is an AE, an abnormal assessment (e.g., ECG finding), a laboratory test abnormality, or a DU complication [Section 3.10.1.9] this information will be recorded as an AE in the eCRF.

- Interruptions should be for less than 10 consecutive days for Period 1 and less than 3 consecutive weeks for Period 2; longer interruptions will lead to permanent discontinuation of study drug and consequently to the EOT for that patient.

- If the patient is prematurely and permanently discontinued from study medication during the Period 1 prior to Week 16 (whatever the reason), all assessments planned at Week 16 (End-of-Period 1) must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug.
• If the patient is prematurely and permanently discontinued from study medication during the Period 2 (whatever the reason), all assessments planned at EOT must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug.

Adverse events will be collected up to 30 days after last dose of study medication.

If discontinuation is study medication-related, the patient will remain under the supervision of the investigator until stabilization of the events.

3.5.2 Patient’s follow-up after study drug discontinuation
All randomized patients who received study drug must undergo all protocol-mandated procedures for Visit 6 (End-of-Period 1) in the event of treatment discontinuation during the Period 1 prior to Week 16, or for EOT in the event of treatment discontinuation during the Period 2 after Week 16. These patients must also be followed-up for 30 days after the last study drug administration via a face-to-face visit (Safety follow-up post-treatment visit) to collect AE/SAE information and to perform liver function testing as well as a pregnancy test (the latter for all females of childbearing potential). In addition, all patients who prematurely and permanently discontinue study drug, either during Period 1 or Period 2, will continue to be followed until EOS according to the visit and assessment schedule. All reasons for study drug discontinuation will be documented in the eCRF.

3.5.3 Study withdrawal
A patient will be considered as withdrawn from the study if, and only if, he/she is lost to follow-up after the investigator was unsuccessful in contacting the patient or if he/she withdraws consent.

3.5.4 Replacement policy
3.5.4.1 Patients
Patients prematurely discontinued from study drug for any reason will not be replaced.

3.5.4.2 Centers
To ensure the successful completion of the study, Actelion may wish to replace centers with no patient enrollment. Centers not able to recruit any patients within 4 months of study initiation will be considered for closure.

3.6 Treatment exposure and compliance
Records of study drug used, dosages administered, and intervals between visits are kept during the study. Study drug accountability is performed on an ongoing basis by the study staff, checked by the monitor during site visits and at completion of the study. Patients are asked to return all unused study drug (including empty bottles) at each visit. At the conclusion of each patient’s participation in the study, all remaining drug supplies
must be returned to the sponsor for an accurate accounting of delivered and returned drugs.

### 3.7 Treatment assignment and blinding

#### 3.7.1 Treatment assignment

Patients will be randomized to one of the treatment groups using a centralized randomization system via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWoRS) provided by an independent service provider. A unique randomization number must be assigned to each patient. Treatment allocation will be stratified by site. Patient randomization will be stratified according to the number of DUs at baseline (≤ 3 and > 3 DUs). The randomization code is to be kept strictly confidential, and accessible only to authorized persons who are not involved in the conduct and analysis of the study, until the time of unblinding. A sealed randomization code is to be kept by the sponsor’s Global Quality Management (GQM) department in a safe cabinet. It is the responsibility of the GQM Assistant to confirm receipt of the sealed randomization code, to secure it in a dedicated fireproof cabinet, to document it in the Quality Management Log of Randomization, and to retain the key to the safe. A second set will be provided to the statistician of the DMC.

The randomization code will be unblinded/broken and made available for data analysis only after study closure, i.e., when the study has been completed, the protocol deviations determined, the clinical database declared complete, accurate, and locked.

#### 3.7.2 Blinding

This study is performed in a double-blind fashion. The investigator and study staff, the patients, the monitors, the sponsor and CRO staff will remain blinded to the treatment until study closure. To guarantee double-blind conditions, each dosage strength of the investigational drug and its matching placebo are indistinguishable with respect to appearance, taste, weight and shape, and all patient bottles will be packaged in the same way.

#### 3.7.3 Emergency procedure for unblinding

The investigator and the study staff must remain blinded to the patient’s treatment assignment, even if the patient refuses to participate in any study procedures or experiences an AE, or if the patient dies. The identity of the study drug may be revealed only if the patient experiences a medical emergency the management of which would be improved by the knowledge of the blinded treatment assignment.

It is possible for the investigator to learn the identity of the study drug dispensed to a patient, based on the subject number, through the centralized randomization system (see site guidelines). If the centralized randomization system is unable to answer, the Medical Hotline (see site guidelines) or Actelion clinical team members (see contact
details on page 2) must be contacted; a set of code-breaks is kept at Actelion and can be used in case of emergency.

The occurrence of any code break during the study must be clearly justified and explained by the investigator.

Before using the IVRS for unblinding, every attempt must be made by the investigator to discuss the intended code break with a representative of Actelion Pharmaceuticals Ltd.

In all cases, the sponsor must be informed as soon as possible before or after the code break.

Any code break must be documented in a detailed report with the date and time of the code break and signed by the investigator.

At the end of the study, before database closure, the monitor will collect the code break reports and return them to Actelion Pharmaceuticals Ltd for reconciliation and filing.

3.8 Study drug packaging, labeling and preparation

3.8.1 Study drug packaging
Study drugs are provided as tablets and supplied in childproof bottles. (More detailed information is given in Section 3.4.1).

3.8.2 Study drug labeling
The study drug labeling complies with the applicable laws and regulations of each country.

3.9 Study endpoints

3.9.1 Efficacy endpoints

3.9.1.1 Primary efficacy endpoint
Cumulative number of new DUs up to Week 16.

3.9.1.2 Imputation methods for efficacy endpoints
Details provided under Section 5.11 (Imputation methods)

3.9.1.3 Other efficacy endpoints
Several additional endpoints are listed below that serve as supportive to the primary analysis, and also provide a means of evaluating consistency of results in this study.
- **Hand Functionality:**
  - i. HDISS-DU
  - ii. HAQ-DI

- **DU Burden:**
  - i. Binary response of patients without a new DU
  - ii. Binary response of patients with more than 1, 2, 3, etc., new DU(s)
  - iii. Total number of DUs observed
  - iv. Time to onset of each new DU (1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th}, etc., DU)

- **DU Complications:** An event of DU complications is defined as the composite of the following:
  - i. Critical ischemic crisis necessitating patient hospitalization.
  - ii. Gangrene, (auto)amputation.
  - iii. Failure of conservative management: Surgical and chemical sympathectomy, vascular reconstructions, or any unplanned surgery in the management of hand manifestation(s).
  - iv. Use of parenteral prostanoids.
  - v. Use of endothelin receptor antagonists.
  - vi. Requiring class II, III or IV narcotics or increase in existing dose of > 50% as compared to baseline.
  - vii. Initiation of systemic antibiotics for the treatment of infection attributed to digital ulceration.

- Patient-reported global assessment of digital ulcer activity (7 point Likert scale).
- Physician-reported global assessment of digital ulcer activity (7 point Likert scale).
- Overall hand pain related to DU(s).
- Scleroderma Health Assessment Questionnaire (SHAQ).
- Work Productivity and Activity Impairment Questionnaire: Digital Ulcer (WPAI:DU).
- Binary response of patients with complete healing of all DU(s).
- Time to complete healing: This is a time-to-event endpoint. Specifically, it is the time it takes for a patient to achieve complete healing of all DUs.
3.9.2 Safety and tolerability endpoints

- Treatment-emergent adverse events (AEs) up to 30 days after last study drug administration.
- Treatment-emergent serious adverse events up to 30 days after last study drug administration.
- Adverse events leading to premature discontinuation of study drug.
- Treatment-emergent marked laboratory abnormalities (MLAs) up to 24 hours after last study drug administration.
- Treatment-emergent electrocardiogram (ECG) abnormalities up to 24 hours after last study drug administration.
- Change from baseline in vital signs (blood pressure and heart rate) up to 24 hours after last study drug administration.
- Occurrence of liver function test (ALT and/or AST) abnormality (> 3 and ≤ 5 × ULN; > 5 and ≤ 8 × ULN; > 8 × ULN) up to 30 days after last study drug administration.

- **The marked** laboratory abnormalities will be assessed for the following laboratory parameters:

**Hematology**

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Erythrocyte count</th>
<th>Differential blood count*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Leukocyte count</td>
<td>Platelet count</td>
</tr>
</tbody>
</table>

*including: basophils, eosinophils, neutrophils, lymphocytes, monocytes

**Biochemistry**

<table>
<thead>
<tr>
<th>Blood chemistry:</th>
<th>Blood liver function tests:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>AST (SGOT)</td>
</tr>
<tr>
<td>Urea</td>
<td>ALT (SGPT)</td>
</tr>
<tr>
<td>Glucose</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>Sodium</td>
<td>Total, direct and indirect bilirubin</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td>Creatinine and creatinine clearance*</td>
<td></td>
</tr>
</tbody>
</table>

*Creatinine clearance will be estimated at screening, Visit 6 (End-of-Period 1) and at EOT visit using the Cockroft-Gault formula.
Cockcroft and Gault equation used utilizes the ideal body weight (IBW) to calculate an estimated creatinine clearance (CRCL).

Cockcroft and Gault equation: CrCl = [(140 – age) × IBW] / (sCr × 72) (× 0.85 for females).

Note: if the actual body weight (ABW) is less than the IBW use the ABW for calculating the CRCL. If the patient is > 65 years old and creatinine < 1.0, use 1 to calculate the creatinine clearance.

3.10 Study assessments

3.10.1 Efficacy assessments

3.10.1.1 Evaluation of digital ulcers

All DUs will be recorded and assessed at each visit to the study center starting with the Screening visit. Only DUs from the proximal inter-phalangeal joint distally (both on the dorsal and volar surface of the hand, including the digital tip) will be recorded. At each planned visit, or in case of premature study drug discontinuation, the location of each new DU since the last visit and assessment of each existing and new DU will be recorded on the eCRF. The total number of DUs as well as the number of new DUs since the last visit will be computed by Actelion. The evaluation will be performed by an experienced physician or trained rater with expertise in the assessment of DU in SSc. The same rater should assess the DUs for a given patient, at each visit whenever possible. Raters will be required to complete training on DU assessment (training material provided by sponsor) prior to conducting these evaluations, as well as acknowledgment of this training by the sponsor, in an effort to improve inter-rater reliability and ultimately harmonize DU assessment across the sites.

In addition, at baseline the location of each DU will be recorded in the eCRF.

DUs reported by the patients and which occurred and healed between visits will not be recorded on the eCRF as new ulcers. Only the ulcers present at the planned visits are counted.

All baseline ulcers and newly occurring DUs during the study will be assessed at every visit for complete healing. Complete healing is defined as complete epithelialization of the ischemic DU regardless of the residual pain.

A “U” will be recorded in the eCRF for each active DU present according to the definition in Section 3.3.2.

A “H” will be recorded for each DU healed according to the definition above.

A “I” will be recorded for each DU in an indeterminate status between a healed DU or a present DU, as defined above.
Indeterminate status will be recorded for a scabbed DU, as the presence of a scab does not allow one to determine conclusively whether a DU is going to heal or to worsen.

Indeterminate status will also be applied for a DU covered by necrotic tissue or in case of deep ischemia of the dermis without a DU at the time of observation.

An ulcer that has developed over a previously healed ulcer will be recorded as a new DU.

**Other skin lesions:**

- Digital pitting scars (small-sized hyperkeratosis) will not be counted within the pool of all DUs present.
- Calcinosis (defined as deposits of calcium phosphate in soft tissues) will not be counted.
- Fissure, paronychia, extrusion of calcium will not be counted.
- Ulcers over the metacarpo-phalangeal joints or elbows will not be counted.

### 3.10.1.2 Scleroderma Health Assessment Questionnaire

The Scleroderma Health Assessment Questionnaire (SHAQ) is used to evaluate change over time of physical disability in patients with SSc [Clements 1999, Clements 2001]. It is comprised of 20 items from the Health Assessment Questionnaire Disability Index (HAQ-DI; a self-administered measure developed to evaluate activities of daily living in arthritis in the past 7 days, covering 8 domains of functional disability (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities) plus 6 patient-rated visual analog scales (VAS) pertaining to individual organ system involvement: vascular problems (Raynaud’s phenomenon), digital ulcers, GI symptoms, breathing problems, overall illness pain, and overall disease severity [Steen 1997]. The SHAQ should be filled out at Randomization, at Week 8, at Week 16 and at EOT.

The tester scores the SHAQ and its VAS.

In the SHAQ, patients are instructed to rate their capacity to perform activities of daily living. This information results in a disability index (DI), which is calculated as a continuous variable from 0 (no disability) to 3 (severe disability).

On the visual analog scales, patients are instructed to score pain, intestinal problems, breathing problems, Raynaud’s phenomenon, finger ulcers, and overall disease severity, marking their symptoms between 0 (no symptoms) and 100 (very severe symptoms). A sample questionnaire and a sample of the VAS scales are shown in Appendix 1.
3.10.1.3 Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI is a self-administered measure developed to evaluate activities of daily living in arthritis. It assesses the patient’s level of functional ability through questions regarding fine movements of the upper extremities, locomotor activities in the lower extremities, and movements of both the upper and lower limbs. It contains the same domains of activity which comprise the SHAQ (dressing, arising, eating, walking, hygiene, reach, grip, and common daily activities) each of which has multiple questions, for a total of 20 items. For each item, patients report the amount of difficulty experienced performing the activity. These will be extracted from the SHAQ (therefore patients do not need to complete a separate HAQ-DI questionnaire). There are four possible responses for each item ranging from 0 (without any difficulty) to 3 (unable to do). A mean score is calculated for each domain ranging from 0 to 3. A composite HAQ-DI score is calculated by dividing the summed domain scores by the number of domains answered. The composite score is reported, falling between 0 and 3 on an ordinal scale. The scores are interpreted as 0 (no impairment in function) to 3 (maximal impairment of function) [Bruce 2003].

The HAQ-DI also contains a visual analog scale (VAS) that patients use to report the amount of pain experienced in the past week (also extracted from the SHAQ). The VAS is a 15-cm line that is converted to a continuous scale from 0 to 3 where 1 cm is equivalent to 0.2 points. The anchors of the VAS are 0 (no pain) to 100 (very severe pain). To obtain the patient score, a metric ruler is used to measure the distance in centimeters from the left anchor to the patient’s mark, and then multiplied by 0.2. The VAS pain score is not incorporated into the HAQ-DI composite score [Steen 1997].

Furthermore, the hand functionality will be assessed using the composite of hand components of the HAQ-DI: grip, hygiene, dressing, eating, and grooming. Both this composite and the HAQ-DI, should be filled out as part of the SHAQ at Randomization, at Week 8, at Week 16 and at EOT.

3.10.1.4 Hand Disability in Systemic Sclerosis – Digital Ulcers (HDISS-DU)

The HDISS-DU was developed in accordance with the FDA Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Label Claims (2009). The concepts and items comprising the HDISS-DU were developed through discussions with expert clinicians, an initial phase of interviews which included concept elicitation and cognitive debriefing on the Cochin Hand Function Scale (an 18-item functional disability questionnaire which uses tasks of daily living to assess function [Duruöz 1996, Mouton 2010, Rannou 2007]), and a second phase of patient cognitive debriefing interviews on a revised instrument. Results from the cognitive debriefing interviews suggest that the HDISS-DU is a comprehensive measure assessing the impact of DU's on hand functioning through 26-items, which ask patients to rate their ability to complete common activities over the past 7 days.
The HDISS-DU is assessed at Randomization, at the four planned visits from Week 4 to Week 16, at the first two quarterly visits in Period 2 (where applicable) and at EOT.

A sample of the HDISS-DU questionnaire is shown in Appendix 2.

### 3.10.1.5 Patient Reported Global Assessment(s) of Digital Ulcer Activity (PGA)

The patient-reported global assessment of DU is assessed at Randomization, at the four planned visits from Week 4 to Week 16.

There are two PGA items:

The first PGA item asks subjects to rate the severity of their digital ulcers, thinking about all the ways the ulcers may have affected them within the past week. The response scale for this item is 7-point Likert scale (1, Not at all; 2, Very mild; 3, Mild; 4, Moderate; 5, Severe; 6, Very severe; 7, Extreme).

The second PGA item is designed to capture patients’ impression of global change in their ulcer disease and asks the patient to rate this change as compared to the time of enrollment, on a 7-point Likert scale (1, Very much worse; 2, Much worse; 3, Minimally worse; 4, No change; 5, Minimally improved; 6, Much improved; 7, Very much improved).

A sample questionnaire is shown in Appendix 3.

### 3.10.1.6 Physician Reported Global Assessment of Digital Ulcer Activity

The physician-reported global assessment of DU is assessed at Randomization (severity of illness only), at the four planned visits from Week 4 to Week 16.

There are two physician-reported global assessments of DU activity: the first assessment, Severity of Illness, assesses the clinician’s impression of the patient’s current digital ulcer disease state. The second assessment, Global Improvement, assesses the patient’s improvement or worsening from the time of randomization (at baseline).

A sample questionnaire is shown in Appendix 6.

### 3.10.1.7 Work Productivity and Activity Impairment Questionnaire: Digital Ulcer V2.0 (WPAI:DU)

The WPAI:DU is assessed at Randomization, at Week 8, Week 16, at the first two quarterly visits in Period 2 (where applicable) and EOT.

The WPAI:DU is a 6 question patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to Digital Ulcer disease during the previous 7 days.

A sample questionnaire is shown in Appendix 4.
3.10.1.8 Overall hand pain related to digital ulcers

Overall hand pain is assessed at Screening, Randomization, at the four planned visits from Week 4 to Week 16.

The patient should complete a global pain item which asks about worst pain in the past week. The response scale for this item is a 1–10 numerical rating scale, with 1 being “no pain” and 10 being “worst pain imaginable.”

A sample scale is shown in Appendix 5.

3.10.1.9 DU complications

DU complications will be assessed at each visit or between visits as appropriate. They are defined as any one of the following, resulting from DU worsening:

i. Critical ischemic crisis necessitating hospitalization.

ii. Gangrene, (auto)amputation.

iii. Failure of conservative management: Surgical and chemical sympathectomy, vascular reconstructions, or any unplanned surgery in the management of hand SSc manifestation(s).

iv. Use of parenteral prostanoids.

v. Use of endothelin receptor antagonists.

vi. Requiring class II, III or IV narcotics or increase in existing dose of > 50% as compared to baseline.

vii. Initiation of systemic antibiotics for the treatment of infection attributed to digital ulceration.

DU complications i–v will result in permanent discontinuation of the study medication. All DU complications will also be captured as AEs.

3.10.2 Safety and tolerability assessments

The definitions, reporting and follow-up of AEs, SAEs and potential pregnancies are described in Section 4.

3.10.2.1 Vital signs

Vital signs (blood pressure and heart rate) will be recorded at every visit starting with screening through EOT. Arterial blood pressure (systolic and diastolic) and heart rate will be measured with the patient both in a supine and standing position. Supine blood pressure and radial pulse should be measured after the patient is in the supine position for a 5-minute period. Standing blood pressure and radial pulse rate should be measured once the patient has been standing for 1 to 3 minutes. While either arm may be used, the position and the arm used for the measurement should be kept constant during the trial
for an individual patient. Also, the same blood pressure cuff should be used for all measurements for a given patient. Pulse rate should be measured after blood pressure measurements.

3.10.2.2 Body weight and height

Body weight is measured at each visit starting with Screening until EOT. Height measurements will only be obtained at the Screening visit (Visit 1).

3.10.2.3 Physical examination

The physical examination will be performed at Screening, at end of Period 1 Visit 6 (Week 16) and EOT.

The physical examination shall be identical to the general medical check-up of SSc patients and comprises a whole body inspection, palpation, percussion, and auscultation. Special investigations/examination methods may also be conducted at the discretion of the investigator to exclude any possible pathological findings.

Significant findings that are present prior to study drug initiation must be recorded on the relevant Medical History eCRF page. Significant findings found after study drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded on the Adverse Event eCRF page.

3.10.2.4 Laboratory assessments

3.10.2.4.1 Type of laboratory

A central laboratory (see Site Guidelines) will be used for all laboratory tests. The central laboratory will send the results to the sponsor electronically.

Laboratory reports will be transmitted to the investigator by fax. All laboratory reports must be dated and signed by the primary investigator or other qualified study personnel at the study site upon receipt, and filed with the source documentation. Any clinically relevant marked laboratory abnormalities that are present at Visit 1 (prior to the start of study drug) must be documented in the medical history section of the eCRF. Any clinically significant marked laboratory abnormalities, occurring after study drug initiation, must be reported by the investigator as an AE and/or SAE as appropriate [Section 4.2], and must be followed until they return to normal range, stabilize, or until the change is no longer clinically relevant. Further laboratory analysis should be performed as indicated and according to the judgment of the investigator.

Any pregnancy occurring during the treatment period and up to 30 days after study drug discontinuation must be reported immediately to the sponsor’s drug safety department using the Pregnancy Form [Section 4.4].
Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormalities can be found in the laboratory manual provided to the investigator.

Laboratory certification / reference ranges are not routinely collected for local laboratories performing routine safety tests that are not intended to be entered into the clinical database. However, if abnormal laboratory values from these local laboratories are assessed as adverse events (as defined in Section 4.2.1) or are obtained to investigate a (serious) adverse event or a pregnancy, the investigator will provide Actelion with these documents.

3.10.2.4.2 Laboratory parameters

- **Complete laboratory tests**
  Complete laboratory tests including standard hematology / biochemistry, liver function tests, and serum pregnancy test (if applicable) will be performed at Screening, at end of Period 1 and EOT. Any of the laboratory parameters may be performed between visits or during the safety follow-up if clinically indicated.

- **Hematology tests** include hemoglobin, hematocrit, erythrocyte, platelet and leukocyte, differential counts and RBC morphology.

- **Blood chemistry** includes measurement of liver aminotransferases (AST/ALT), alkaline phosphatase, total, direct and indirect bilirubin, creatinine, urea (or blood urea nitrogen [BUN]), glucose, sodium, potassium, magnesium, albumin as well as creatinine and creatinine clearance.

- **Hemoglobin concentration:** Hemoglobin concentration must be checked at Screening, and during the treatment period every 4 weeks starting with Visit 3 (Week 4) until and including EOT visit. If a clinically relevant decrease in hemoglobin concentration occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment.

- **Pregnancy test**
  For women of childbearing potential, a serum pregnancy test must be performed at Screening, and every 4 weeks thereafter up to 30 days after the last treatment dose. This test may also be performed at anytime if pregnancy is suspected during the study. In addition, a urine pregnancy test should be performed at Visit 2, if Visit 1 was done more than 5 days before Visit 2. A urine pregnancy test will be performed at any additional unscheduled visit to the study center during the treatment period, using dipsticks.

  The results will not be collected in the eCRF. In the event of pregnancy, a Pregnancy Form must be completed [Section 4.4.2].
• **SSc serology**
  SSc serology will be collected at randomization (Visit 2). ANA subset tests anti-Scl 70 Ab, and anti-centromere Ab will be performed. In addition, antibodies against angiotensin II type 1 receptor and endothelin-1 type A receptor will be performed.

• **Liver function tests monitoring and study treatment adjustments**
  
  o **Liver aminotransferase monitoring in all patients**
    Liver aminotransferase levels (alanine and aspartate aminotransferases), will be measured as part of liver function tests (LFTs) which will also include alkaline phosphatase, and bilirubin (direct and indirect). LFTs must be measured at screening, every 4 weeks during the treatment period starting with Visit 3 (Week 4) until and including the post-treatment (safety follow-up)/EOS visit 30 days after study drug discontinuation.
Study treatment adjustment in case of ALT and/or AST elevations

<table>
<thead>
<tr>
<th>ALT and/or AST</th>
<th>Treatment and monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 and ≤ 8 × ULN</td>
<td>Interrupt study medication. Perform a re-test adding total and direct bilirubin and alkaline phosphatase measurements. If confirmed, continue to monitor aminotransferase, bilirubin and alkaline phosphatase levels weekly until values return to pre-treatment levels. If the aminotransferase values return to pre-treatment levels, re-introduction of study treatment can be considered. Interruptions should be for less than 10 days; longer interruptions should lead to permanent discontinuation of study drug. Re-introduction of study treatment after treatment interruption should only be considered if the potential benefits of treatment with macitentan outweigh the potential risks and when liver aminotransferase values are within pre-treatment levels. The advice of a hepatologist is recommended. Liver aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks and thereafter according to the recommendations above (i.e., at monthly intervals).</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal.

In case of aminotransferases > 3 × ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), or in case of aminotransferases ≥ 3 × ULN associated with increases in total bilirubin ≥ 2 × ULN or in case of aminotransferases > 8 × ULN, treatment must be stopped and re-introduction of study treatment is not to be considered. Aminotransferase, bilirubin and alkaline phosphatase levels must be monitored weekly after study drug discontinuation until values return to pre-treatment levels.

Other diagnoses should be considered and ruled out by performing the appropriate tests (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus, etc.).

All LFT abnormalities leading to study drug interruption or discontinuation must be recorded as AEs [Section 4.2.4].

During this study, an independent Data Monitoring Committee (DMC) will review unblinded safety and tolerability clinical data at regular intervals to monitor patient safety. Additionally, an independent International Liver Safety Board (ILSB), organized
by Actelion Global Drug Safety, and which is composed of an external expert committee of hepatologists, will provide ongoing assessment and advice regarding all hepatic events that may occur during the use of macitentan across all studies. The ILSB will receive individual liver case reports of interest for expert review. Any potential signals from the use of macitentan will be discussed with the ILSB in order to establish their importance and to suggest further steps. In order to ensure their proper and comprehensive evaluation, additional patient data may be collected in a liver questionnaire, and subsequently these data may be integrated in the form of narrative(s).

3.10.2.4.3 ECG
A standard 12-lead ECG will be performed at Screening, at end of Period 1 (Visit 6) and EOT. If clinically indicated, it may also be performed during the safety follow-up. The patient should rest for at least 5 minutes prior to the recording, and should be in a resting position during the recording.

Significant findings that are present prior to the start of the study drug must be documented in the Medical History section of the eCRF.

Clinically significant ECG findings found after the study drug initiation and that were not present at screening or that worsened during the study must be reported as an AE [Section 4.2].

3.10.3 Baseline parameters and concomitant medications

3.10.3.1 Baseline demographics and disease characteristics
Demographics (age, race, height, weight, sex), medical history and disease characteristics will be recorded. It includes information required for inclusion purposes and part of the SSc-specific medical status: ACR criteria for SSc, extent of skin involvement i.e., limited or diffuse type, SSc serology (to be collected at Randomization), age at time of SSc diagnosis, delay between RP onset and first non-RP clinical symptom, time since first non-RP symptom onset, age at first non-RP symptom, environmental/occupational risks, time since diagnosis of DUs and RP, smoking history [Harrison 2002].

3.10.3.2 Concomitant medications
Concomitant medications, including topical treatments for the treatment of SSc, DUs, Raynaud’s phenomenon or any concomitant disease taken between 3 months prior to randomization and EOT will be recorded on the Concomitant Medication section of the eCRF.

Concomitant medications initiated or stopped for an AE or any other reason will be recorded on the Concomitant Medication/Adverse Event pages (as appropriate) of the eCRF.
For patients who prematurely and permanently discontinued study drug and continued to be followed until EOS, only medications prescribed for DU and systemic sclerosis (including analgesics) will continue to be collected.

### 3.11 Visit and assessment schedule

Patients will come to the clinic for the following visits:

- Screening
- Randomization
- Every 4 weeks during the 16-week Period 1. In Period 2, visit frequency is every month for laboratory determinations and every three months for other assessments.

*Table 1* provides an overview of the chronological sequence of the assessments. The visit window is ± 1 week during both period 1 and period 2. However, the interval between any 2 successive visits in period 1 is not to exceed 36 days in total. Planned visit dates are from the day of randomization.

Study medication will be dispensed at Randomization, and at Week 4, 8, 12, 16 visits (in Period 1), and every 3 months thereafter (in Period 2) for all patients.

Liver function and hemoglobin tests must be performed at screening, and every 4 weeks after study drug initiation, until EOT for the hemoglobin test and 30 days after study drug discontinuation for the liver function tests (at the post-treatment safety follow-up/EOS visit), and in case of premature study treatment discontinuation. Serum pregnancy tests (for women of childbearing potential) must be performed at Screening, and every 4 weeks after study drug initiation, until 30 days after study drug discontinuation (at the post-treatment safety follow-up/EOS visit). A urine pregnancy test will also be performed (for women of childbearing potential) at Randomization (Visit 2), if Screening (Visit 1) was done more than 5 days before Visit 2.

Evaluation of DU (total number of DU, occurrence of new DU, healing of all DU, baseline DUs and new DUs and location of DUs) is performed at each visit, starting with the screening visit.

At each visit, the investigator will make recommendations to the patients that include protecting the hands from cold, avoiding strenuous hand work and stressful situations.

#### 3.11.1 Visit 1 (Screening visit)

It is the responsibility of the investigator to obtain written informed consent from each patient participating in the study after adequate explanation of the aims, methods, objectives and potential hazards of the study. The informed consent form of the patients wishing to participate in the study has to be signed at the Screening visit prior to the screening examination and any study specific procedure.
The Screening visit should include:

- Patient information and consent form signature
- Review of inclusion/exclusion criteria
- Recording of demographics (age, race, height, weight, sex), medical history and disease characteristics. It includes information required for inclusion purpose and part of the SSc-specific medical status: ACR criteria for SSc or CREST criteria, extent of skin involvement i.e., limited or diffuse type, time since diagnosis of SSc, DUs, and Raynaud’s phenomenon
- Physical examination
- All laboratory tests: (including pregnancy test for women of childbearing potential)
- Height and weight measurements
- Measurement of vital signs (blood pressure and heart rate)
- 12-lead ECG
- Assessment of concomitant disease/medication
- Recording of the location, date of appearance and assessment of each DU
- Patient’s assessment of overall hand pain related to DU
- Serious adverse events related to study mandated procedures only after signature of informed consent and before study drug administration

The investigator will check all the inclusion/exclusion criteria assessed at Visit 1 and decide on the potential eligibility of the patient. Re-screening is allowed once, but all assessments for a given patient should be repeated, excluding labs and ECG if initial set performed within the previous 2 weeks.

Should the laboratory tests show that the results are within the acceptable ranges defined in the eligibility criteria, the patient may be randomized within 2 weeks of the Screening visit, providing all other inclusion/exclusion criteria are met.

Screening and Randomization visits may be performed on the same day if the patient meets all study criteria and has documented local laboratory test results on this day. In addition, complete laboratory tests must be sent for analysis to the central laboratory.

3.11.2 Visit 2 (Randomization visit)
The Randomization visit is performed as soon as possible after the Screening visit up to a maximum of 14 days. At this visit (study Day 1) patients will be randomized to either 3mg, or 10 mg q.d. macitentan, or placebo (1:1:1 ratio).
It is suggested that during a given visit, the HDISS-DU should be performed before any other assessment(s), followed by the SHAQ.

The Randomization visit should include:

- Review of inclusion/exclusion criteria
- Recording of SSc-specific medical status if not done at screening: ACR criteria for SSc or CREST criteria, extent of skin involvement i.e., limited or diffuse type, time since diagnosis of SSc, time since diagnosis of DUs and Raynaud’s phenomenon
- Measurement of vital signs (blood pressure, heart rate)
- SSc serology
- Urine pregnancy test, in women of childbearing potential, if Visit 1 was performed more than 5 days before Visit 2.
- Body weight measurement
- Recording of the location, date of appearance and assessment of each DU
- DU complication assessment
- Patient’s assessment of overall hand pain related to DU
- Self-administered Scleroderma Health Assessment Questionnaire (SHAQ)
- Hand Disability in Systemic Sclerosis – Digital Ulcers (HDISS-DU)
- Self-administered Work Productivity and Activity Impairment Questionnaire: Specific Health problems (WPAI:DU)
- Patient-reported global assessment
- Physician-reported global assessment
- Adverse events
- Recording of concomitant medications taken by the patient since screening
- Dispensing of study medication, the patient must bring back the bottle at the next visit.

3.11.3 Visits 3, 4 and 5 (Weeks 4, 8 and 12 ± 1 week)

Each of these visits should include the recording of:

- Adverse events, vital signs, body weight and changes in concomitant medications
- The location and the assessment of each new DU (time period from last visit to the current visit)
• The assessment of each previous DU
• DU complication assessment
• Patient’s assessment of overall hand pain related to DU
• Self administered HDISS-DU
• Self-administered SHAQ (Week 8 only)
• Self administered WPAI:DU(Week 8 only)
• Patient-reported global assessment
• Physician-reported global assessment
• Liver function tests (alanine and aspartate aminotransferases, alkaline phosphatase, bilirubin direct and indirect), hemoglobin and pregnancy test (for women of childbearing potential)
• Dispensing/return of study medication

3.11.4 Visit 6 (Week 16 ± 1 week) (End-of-Period 1 and entry into Period 2)
Visit 6 should include the recording of:
• Physical examination
• Adverse events, vital signs, body weight and changes in concomitant medications
• The location and the assessment of each new DU (time period from last visit to the current visit)
• The assessment of each previous DU
• DU complication assessment
• All laboratory tests: (including pregnancy test for women of childbearing potential)
• 12-lead ECG
• Patient’s assessment of overall hand pain related to DU
• Self-administered SHAQ
• Self-administered HDISS-DU
• Self administered WPAI:DU
• Patient-reported global assessment
• Physician-reported global assessment
• Dispensing/return of study medication
• In the event of treatment discontinuation during the Period 1 prior to Week 16 (whatever the reason), all assessments planned at Visit 6 (End-of-Period 1) must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug.

3.11.5 Visits 7, 8, 9… (Visits every month ± 7 days for laboratory determinations and Visits every 3 months ± 7 days for all other assessments)

Visit 7, 8, 9… should include the recording of:

Monthly assessments (Every month ± 7 days) Visits 7, 8, 10, 11 etc:

• Laboratory determinations: Liver function tests (alanine and aspartate aminotransferases, alkaline phosphatase, bilirubin direct and indirect, hemoglobin and pregnancy test (for women of childbearing potential)

Quarterly assessments (Every 3 months ± 7 days) Visits 9, 12, 15 etc:

• Adverse events, vital signs, and changes in concomitant medications
• Body weight measurement
• The location and the assessment of each new DU (time period from last visit to the current visit)
• The assessment of each previous DU
• DU complication assessment
• Self administered HDISS-DU at the first two quarterly visits only
• Self administered WPAI:DU at the first two quarterly visits only
• Dispensing/return of study medication

3.11.6 EOT Visit ± 7 days)

EOT for all ongoing patients is defined as the timepoint when the last randomized patient, not prematurely withdrawn, has completed the 16-week Period 1.

This visit may not need to be performed if end-of-period 1 (Visit 6) was performed within 1 week of the official EOT.

EOT Visit should include the recording of:

• Physical examination
• Adverse events, vital signs, body weight and changes in concomitant medications
• The location and the assessment of each new DU (time period from last visit to the current visit)
• The assessment of each previous DU
• DU complication assessment
• All laboratory tests: (including pregnancy test for women of childbearing potential)
• 12-lead ECG
• Self-administered SHAQ
• Self-administered HDISS-DU
• Self administered WPAI:DU
• Return of study medication
• In the event of treatment discontinuation during the Period 2 (whatever the reason), all assessments planned at EOT must be performed as soon as possible but no later than 7 days following the date of the last dose of study drug.

3.11.7 Post-Treatment (Safety Follow-up)/EOS visit (30 days after study drug discontinuation)

• Visit will include:
  • Liver function tests (alanine and aspartate aminotransferases, alkaline phosphatase, bilirubin direct and indirect), and pregnancy test (for women of childbearing potential)
  • The location and the assessment of each new DU (time period from last visit to the current visit)
  • The assessment of each previous DU
  • Concomitant medications (only those related to DU or SSc)
  • DU complication assessment
  • Adverse events

The EOS will occur when the last randomized patient, not prematurely withdrawn, who has completed Period 1, completes the 30-day post treatment follow-up visit.

3.11.8 Visits a, b, c… (Visits every 3 months ± 7 days): For patients who have prematurely and permanently discontinued

Visits a, b, c… should include the recording of:

• The location and the assessment of each new DU (time period from last visit to the current visit)
• The assessment of each previous DU
• Concomitant medications (only those related to DU or SSc)

• DU complication assessment

All patients who prematurely and permanently discontinue study drug during either Period 1 or Period 2 (except those who have withdrawn their consent, or are lost to follow-up), will complete the Post-Treatment Visit 30 days after study drug discontinuation, and will continue to be followed every 3 months thereafter until EOS.

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Summary table

<table>
<thead>
<tr>
<th>Periods</th>
<th>Screening</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>After follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time frame</td>
<td>From signature of informed consent to study drug initiation</td>
<td>During study drug administration plus 24 hours</td>
<td>From 24 hours until 30 days after study drug discontinuation</td>
<td>After 30 days</td>
</tr>
<tr>
<td>AE/SAE reporting on eCRF AE page</td>
<td>None</td>
<td>All AEs/SAEs (treatment-emergent)</td>
<td>All AEs/SAEs</td>
<td>None</td>
</tr>
<tr>
<td>SAE reporting on SAE form</td>
<td>Only if related to study-mandated procedures</td>
<td>All SAEs (treatment-emergent)</td>
<td>All SAEs</td>
<td>If felt appropriate by investigator</td>
</tr>
<tr>
<td>Reconciliation ¹</td>
<td>Not applicable</td>
<td>Yes</td>
<td>Yes</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Clinical study report</td>
<td>Might be described</td>
<td>Analyzed</td>
<td>Analyzed</td>
<td>Might be described</td>
</tr>
</tbody>
</table>

¹ Reconciliation between clinical and drug safety databases.

4.2 Adverse events

4.2.1 Definitions of adverse events

An AE is any adverse change from the patient’s baseline condition, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the course of the study, whether or not considered related to the study drug.

A treatment-emergent AE is any AE temporally associated with the use of a study drug (from study drug initiation until 30 days after study drug discontinuation), whether or not considered related to the study drug.
Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalizations for elective cosmetic surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

### 4.2.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.
If an AE occurs during a washout or placebo run-in phase and afterwards worsens during
the treatment phase, a new AE page must be filled out with the intensity observed during
study drug administration.

The three categories of intensity are defined as follows:

- **Mild**
  The event may be noticeable to the patient. It does not influence daily activities, and
  usually does not require intervention.

- **Moderate**
  The event may make the patient uncomfortable. Performance of daily activities may be
  influenced, and intervention may be needed.

- **Severe**
  The event may cause noticeable discomfort, and usually interferes with daily activities.
  The patient may not be able to continue in the study, and treatment or intervention is
  usually needed.

A mild, moderate, or severe AE may or may not be serious [Section 4.3.1]. These terms
are used to describe the intensity of a specific event (as in mild, moderate, or severe
myocardial infarction). However, a severe event (such as severe headache) may be of
relatively minor medical significance and is not necessarily serious. For example, nausea
lasting several hours may be rated as severe, but may not be clinically serious. Fever of
39 °C that is not considered severe may become serious if it prolongs hospital discharge
by a day [Section 4.3.1.2]. Seriousness rather than severity serves as a guide for defining
regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test
abnormalities or abnormal assessments (e.g., ECG findings) considered as AEs. The
investigator should tick “non-applicable” on the AE page of the eCRF to qualify the
intensity of the AE.

### 4.2.3 Relationship to study drug

Each adverse event must be assessed by the investigator as to whether or not there is a
reasonable possibility of causal relationship to the study drug, and reported as either
related or unrelated.

- **Related to study drug**
  This category applies to any AE (whether serious or not) that appears to have a
  reasonable possibility of causal relationship to the use of the study drug (i.e., a
  relationship cannot be ruled out). Guidelines to determine whether an event might be
  considered related include (but are not limited to) the following:
• The event occurred in close temporal relationship to study drug administration.
• The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted, or discontinued.
• The event reoccurred when treatment was reintroduced.
• Environmental factors such as clinical state and other treatments could equally have caused the event.

☐ **Unrelated to study drug**

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).

### 4.2.4 Reporting of adverse events

All AEs occurring after study drug initiation and up to 30 days after study drug discontinuation must be recorded on the AE pages of the eCRF.

### 4.2.5 Follow-up of adverse events

Adverse events still ongoing after study drug discontinuation for a given patient must be followed until 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained.

### 4.3 Serious adverse events

#### 4.3.1 Definitions

##### 4.3.1.1 Serious adverse events

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring inpatient hospitalization, or prolongation of existing hospitalization
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically significant, or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the sponsor to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the Investigator’s Brochure [ACT-064992 IB].

4.3.1.2 Hospitalization – prolongation of existing hospitalization

The following reasons for hospitalizations are not considered AEs, and are therefore also not SAEs:

- Hospitalizations for elective cosmetic surgery, or social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., elective hip replacement for arthritis. Complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

4.3.1.3 Serious adverse events related to study-mandated procedures

An SAE is defined as related to study-mandated procedures if it appears to have a reasonable possibility of a causal relationship (i.e., a relationship cannot be ruled out) to such a procedures (other than administration of study drug). Examples of study-mandated procedures include discontinuation of a patient’s previous treatment during a washout period, complication of a mandated invasive procedure such as blood sampling or heart catheterization, car accident on the way to the hospital for a study visit, etc.

4.3.2 Reporting of serious adverse events

4.3.2.1 Screening period

Serious adverse events occurring between signing the Informed Consent Form and study drug initiation are only required to be reported if they are considered by the investigator to be related to study-mandated procedures.

As these SAEs are not reported as AEs in the eCRF, they are collected only on an SAE form, and entered only into the drug safety database.
4.3.2.2 Treatment period

All SAEs, regardless of causal relationship, must be reported, including those related to study-mandated procedures. Those SAEs occurring during study drug administration, i.e., between study drug initiation and up to 30 days after study drug discontinuation, are defined as treatment-emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the eCRF. They are therefore entered into both the drug safety and clinical databases, and must be reconciled before study closure.

4.3.2.3 Follow-up period

All SAEs regardless of causal relationship occurring until 30 days after study drug discontinuation must be recorded on an SAE form and eCRF.

4.3.2.4 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator’s first knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the patient, and whether or not this event is considered by the investigator to be related to study drug.

These SAE forms must be faxed to the Actelion drug safety department [see contact detail on page 2]. The investigator must complete the SAE form in English (unless otherwise specified), and must assess the relationship of the event to study drug.

Such preliminary reports will be followed by detailed descriptions that may include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion Drug Safety department may contact the investigator to obtain further information.

Suspected (considered related to the study drug) and unexpected (not previously described in the Investigator’s Brochure [ACT-064992 IB] serious adverse reactions (SUSARs) will be expedited by Actelion to Health Authorities, ECs/IRBs and investigators, as appropriate. Unblinding of SUSARs will be performed as appropriate.

However, these events, as with all safety data, will be monitored during the study by the DMC.

4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the post-treatment/EOS visit must be followed up until resolution or stabilization, or until the event is otherwise explained.
4.3.4 After the 30-day follow-up period

New SAEs occurring at any time after the 30-day follow-up period after study drug discontinuation should be reported to the Actelion Drug Safety department within 24 hours of the investigator’s knowledge of the event, if considered causally related to previous exposure to study medication by the investigator. These SAEs are only entered in the drug safety database, and hence will not affect study closure.

4.4 Pregnancy

4.4.1 Teratogenicity

Due to the potential teratogenicity of macitentan, women of childbearing potential must take appropriate precautions, and must not become pregnant during the study and for up to 30 days after study drug discontinuation.

If a patient becomes pregnant, or if pregnancy is suspected, the study drug must be immediately withheld until the result of a laboratory pregnancy test is available. Should pregnancy be confirmed, the patient must be discontinued from the study, and the sponsor must be notified within 24 hours. The treatment code must be broken, and if the patient was on active treatment the investigator must counsel the patient and discuss the risks of continuing with the pregnancy, and the possible effects on the fetus.

4.4.2 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring during study drug administration or during the 1 month following study drug discontinuation must be reported within 24 hours of the investigator’s knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to Actelion Global Drug Safety (see contact details provided on the pregnancy form), and on an AE page of the eCRF, as applicable.

4.4.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to Actelion Global Drug Safety.

Such follow-up information will only be entered in the drug safety database, and hence will not affect study closure.

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be written and finalized before study closure, i.e., database closure and unblinding of the randomization code. The SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.
The SAP will include the definition of major and minor protocol deviations and the link between major protocol deviations and the analysis sets. Major and minor protocol deviations will be identified together with medically trained staff before database lock.

This section in the protocol is dedicated to listing the various analyses proposed and the main methods and approaches to be deployed in the final analysis of study data upon database release.

5.2 Symbol glossary
The following symbols will be used to define various analyses:

1. \( DU3 = \begin{cases} 0, & \text{if } \leq 3 \text{ DU}3 \text{ s at baseline} \\ 1, & \text{if } > 3 \text{ DU}3 \text{ s at baseline} \end{cases} \)
2. Counts up to Week 16: Count_W16
3. Counts up to EOT: Count_EOT
4. Counts up to 7 days after the EOT: Count_EOT7
5. Change from baseline to Week 16: BL_W16
6. Change from Week 16 to EOT: W16_EOT
7. Change from baseline to EOT: BL_EOT
8. Proportion of patients up to Week16: p_W16
9. Proportion of patients up to EOT: p_EOT

5.3 Analysis sets
Three different analysis sets are defined for statistical evaluation as follows:

- **Safety set (S)**
  This analysis set includes patients who were randomized, and received study drug at least once.

- **Modified intent-to-treat set (mITT)**
  This analysis set includes all randomized patients who received at least one dose of the study drug and had at least one post-baseline efficacy assessment.

- **Per-protocol set (PP)**
  This analysis set includes all patients in the mITT set who did not violate the protocol in a way that could influence the primary efficacy outcome. These set will be identified before database lock.
5.4 Endpoints

5.4.1 Primary efficacy endpoint
The primary endpoint is the cumulative number of new DUs up to Week 16.

5.4.2 Other efficacy endpoints
Several additional endpoints are listed below that serve as supportive to the primary analysis, and also provide a means of evaluating consistency of results in this study.

- **Hand Functionality:**
  i. HDISS-DU
  ii. HAQ-DI

- **DU Burden:**
  i. Binary response of patients without a new DU
  ii. Binary response of patients with more than 1, 2, 3, etc., new DU(s)
  iii. Total number of DUs observed
  iv. Time to onset of each new DU (1st, 2nd, 3rd, 4th, etc., DU)

- **DU Complications:** An event of DU complications is defined as the composite of the following:
  i. Critical ischemic crisis necessitating patient hospitalization
  ii. Gangrene, (auto) amputation
  iii. Failure of conservative management: Surgical and chemical sympathectomy, vascular reconstructions, or any unplanned surgery in the management of hand manifestation(s)
  iv. Use of parenteral prostanoids (for the purpose of treatment, not prevention)
  v. Use of endothelin receptor antagonist
  vi. Class II, III or IV narcotics: either initiation, or a total increase in dose of > 50% when compared to that at baseline
  vii. Initiation of systemic antibiotics for the treatment of infection attributed to digital ulceration
• Binary response of patients with complete healing of all DUs
• Time to complete healing: this is a time-to-event endpoint. Specifically, it is the time it takes for a patient to achieve complete healing of all DUs
• Patient-reported global assessment of digital ulcer activity (7 point Likert scale)
• Physician-reported global assessment of digital ulcer activity (7 point Likert scale)
• Overall hand pain related to DU(s)
• SHAQ
• WPAI:DU

5.5 Statistical analysis

5.5.1 Analytical approaches for statistical analyses/inference
Unless otherwise stated, the following analytical methods will be used when analyzing various types of data in this study. Model details, specifications and diagnostic approaches will be outlined in the SAP.

• Counts data will be analyzed using the negative-binomial regression model (NB2), with DU3 as a covariate, for the comparison of each active dose versus placebo. Means and % reduction in mean counts will be presented.
• Continuous data will be analyzed using an analysis of covariance (ANCOVA) model with DU3 as a covariate, for the comparison of each active dose versus placebo. LSMeans of comparisons will be presented.
• Binary data will be analyzed using a logistic regression model (LOGISTIC) with DU3 as a covariate, for the comparison of each active dose versus placebo. Appropriate odds ratios and corresponding 95% CIs will be presented.
• Time to event data will be analyzed using the Cox’s proportional hazards model (COX) with DU3 as a covariate, for the comparison of each active dose versus placebo. The proportional hazards assumption will be tested. In the event of non-proportionality, appropriate measure/s will be taken. In addition, Kaplan Meier (KM) curves will be presented as needed. Appropriate hazard ratios, their corresponding 95% CIs, along with KM estimates will be presented.
• Time to multiple events will be analyzed using the Wei–Lin–Weissfeld (WLW) method attributed to Wei et al. [Wei 1989]. Relevant p-values will be presented.
5.5.2 Primary hypotheses
The global null hypothesis is expressed as a family of two (nested) null hypotheses corresponding to the difference of the high-dose and of the low-dose, respectively, versus placebo on the primary endpoint [Section 5.4.1].

The primary hypothesis will be evaluated using a NB2 model on the counts of new DUs. The NB2 model was chosen to perform the primary analysis in order to be able to incorporate the baseline stratification covariate (e.g., DU3).

5.5.3 Sample size
A reduction of 45% from the expected 4.4 new ulcers per patient in the placebo group (extrapolated from the RAPIDS-2 study) to 2.4 new ulcers per patient in the bosentan group is considered to be clinically relevant.

Hence, under the following assumptions:

- negative-binomial distribution (NB2)
- mean number of new DUs on placebo of 4.4
- mean number of new DUs on macitentan (high-dose) 2.4
- overdispersion parameter of 0.76 (based on the RAPIDS studies)
- 10,000 simulation runs

95 patients per group provide a power of ~97% for the comparison of high-dose versus placebo when using the NB2 model. Power for performing the model-independent Pitman’s permutation test, with the above sample size, is 90%.

5.5.4 Primary endpoint analyses
5.5.4.1 Digital ulcers assessments
When more than one value is obtained after Screening, the last available value up to and including the time of study drug initiation is used as the baseline value. Imputation methods for the substitution of incomplete, missing, or potentially biased data are defined in Section 5.11.

For the cumulative number of new DUs, patients will be considered completers if all assessments up to Week 16 fall within the treatment period [Section 3.11].

5.5.4.2 Main analysis
The main analysis on the primary efficacy endpoint will be carried out on the mITT set [Section 5.3] using a NB2 [Section 5.5.1] model, with DU3 as a covariate, for the comparison of each active dose versus placebo. Both crude and model-based means
differences, together with the corresponding 95% CIs, on the number of new DUs will be presented. Percent reduction in the mean number of new DUs will also be presented.

5.5.4.3 Dose-response exploration

Assuming that there exists a (non-zero) dose-response relationship between the 3 mg and 10 mg groups (in the slope of the dose-response relationship), the formal inferential testing will be carried out using a closed testing procedure as specified in Dunnett [Dunnett 1955]. Dunnett’s method controls for the overall family-wise-error rate (FWER) for pairwise-multiple comparisons versus placebo. Dunnett’s procedure will be executed on the model based pairwise comparison between the active dose groups and placebo. Methodological details will be presented in the SAP. This procedure will enable an ordering of the dose groups, while controlling for the overall Type I error.

5.5.4.4 Sensitivity (to the primary) analyses

The following sensitivity analyses of the primary efficacy endpoint will be carried out for robustness of results:

- **Per-protocol analyses:** The primary analysis will be carried out on the PP set, using the same statistical methods applied for the main analysis.

- **Without stratification factor:** The primary analysis will be carried out using a NB2 [Section 5.5.1] model, without DU3 as a covariate, for the comparison of each active dose versus placebo, on the mITT set.

- **Pitman’s Permutation test:** Pitman’s test on raw DU counts for the comparison of each active dose versus placebo will be carried out on the mITT set.

5.5.5 Supportive analyses

Analytical approaches for each of the other endpoints [Section 5.4.2] are outlined below:

1. **Hand Functionality**
   a. BL_W16, and BL_EOT analyses will be carried out using ANCOVA on overall (aggregate) HDISS-DU, as well as its components.
   b. BL_W16, BL_EOT, and W16_EOT analyses will be carried out using ANCOVA on the overall/composite, as well as components of HAQ-DI.

2. **DU Burden**
   a. **Patients without a new DU:** LOGISTIC model will be used on the binary response at Week 16. In addition, p_W16 will be summarized.
   b. **Patients with more than 1, 2, 3, etc., new DU(s):** Summarized with p_W16 and p_EOT.
   c. **Total number of DUs observed:** NB2 will be used on the change in the count of the total number of DUs between baseline and Week 16.
d. **Time to onset of each new DU (1st, 2nd, 3rd, 4th, etc., DU):** time to 1st new DU will be analyzed using COX. Time to multiple new DUs will be also analyzed using the WLW method. All times (2nd, 3rd, etc.) will be summarized by randomized groups.

3. **DU complications:** Composite, and its individual components, will be analyzed as follows:
   a. Binary responses will be analyzed using LOGISTIC at EOT7.
   b. Time to 1st complication will be analyzed using COX (time calculated up to 7 days after EOT – EOT7).

4. Patients who experienced **complete healing** at Week 16, and EOT will be analyzed using LOGISTIC. Additionally, time to complete healing (censored at EOT) will be analyzed using COX.

5. **Patient-, and physician-reported global assessment of digital ulcer activity** will be analyzed using:
   a. Time profiles by randomized groups.
   b. BL_W16 will be analyzed using ANCOVA.

6. BL_W16 on **overall hand pain** will be analyzed using ANCOVA.

7. **Patients without a new DU** at EOT will be analyzed using LOGISTIC.

8. BL_W16, BL_EOT, and W16_EOT analyses will be carried out using ANCOVA on the overall/composite, as well as components of SHAQ, and **WPAI_DU**, each.

5.6 **Safety and tolerability endpoints**

5.6.1 **Overall**

Safety and tolerability analyses will be carried out descriptively on the safety set.

The analysis of safety will be carried out for the overall treatment period by treatment group. All AEs and SAEs are coded using the MedDRA dictionary.

Patients with at least one treatment-emergent AE will be tabulated by system organ class (SOC), and individual preferred terms within each SOC. The crude incidence of patients who experienced AEs coded with the same preferred term will be tabulated by treatment group (in descending order according to the incidence in the investigational study drug group). Patient with AEs will also be summarized by worst severity and by relationship to study drug.

Number of patients with AEs leading to premature discontinuation of study drug will be summarized in a similar manner to that used for AEs.
Patients with treatment-emergent SAEs will be listed and summarized in a similar manner to that used for AEs, separated into treatment-emergent SAEs, and SAEs occurring before study drug initiation and after study drug discontinuation.

Reasons for death will be listed and summarized in a similar manner to that used for AEs, separated into treatment-emergent deaths, and deaths occurring before study drug initiation and after study drug discontinuation.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables.

Changes from baseline in vital signs (blood pressure and heart rate) and body weight will be summarized by computing the usual location and scale statistics by period and treatment group for the absolute values, and for the change from baseline.

Patients with treatment-emergent ECG abnormalities will be summarized by treatment group and presented in a similar manner to that used for AEs. Absolute values and changes during the course of the study in ECG numeric parameters will be summarized by computing the usual location and scale statistics by period and treatment group.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory parameter by treatment group providing their incidence and frequency. Actelion internal guidelines will be used for the definition of marked laboratory abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory parameters will be transformed into standard units. Absolute values and changes during the course of the study in laboratory parameter values converted to standardized units will be summarized by computing the usual location and scale statistics by period and treatment group.

All safety assessment will be presented in subject listings.

5.6.2 DU complications
DU complications as defined in Section 3.9.1.3, will be collected in a fashion that facilitates their partition into a set associated with DUs at baseline, and thus the reminder associated with new DUs (primary endpoint). DU complications will be summarized separately by their association to baseline and new DUs.

5.7 Exposure to study drug
Exposure to study drug(s) will be described in terms of duration and dose. The duration of exposure is defined as the time elapsing between study drug initiation and discontinuation of study drug, inclusive. The exposure time will be tabulated using the usual location and scale statistics by treatment group. The cumulative distribution of exposure time by different class intervals (e.g., at least 4 weeks, at least 8 weeks, etc.)
will be tabulated to show the number and percentage of patients in each class interval. The mean daily dose per patient is defined as the ratio between the total study drug dose administered during the treatment period and the total exposure time. The mean daily dose is tabulated using the usual location and scale statistics by treatment group.

5.8 Baseline parameters and concomitant medications
Continuous demographic variables (e.g., age, height, weight) and disease characteristics (e.g., onset date) will be summarized by the usual location and scale statistics.

Qualitative demographic characteristics (e.g., gender, race, geographic location, smoking history) and disease characteristics (e.g., etiology, concomitant medications at baseline) will be summarized by counts and percentages. Other baseline patient characteristics (e.g., medical history, previous medications,) will only be listed.

Distributions of these parameters will only be compared descriptively between the treatment groups. No statistical inference will be performed.

Previous and concomitant medications will be coded according to the WHO drug code and the ATC class code. They will be summarized by type (e.g., previous, concomitant, for AE) by tabulating the number and percentages of patients having received each treatment.

5.9 Exploratory analyses
Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

5.10 Interim analyses
No interim efficacy analysis is planned. During this study, a DMC will review unblinded safety and tolerability clinical data at regular intervals to monitor patient safety.

The DMC is empowered to recommend modifications to the protocol to enhance patient safety, or to recommend early termination of the study if major concerns arise about the patients’ safety at any time during the course of this study, or during any other study with the same investigational drug. There is no limit to the number and timing of interim analyses which have the aim of guaranteeing the safety of the patients.

5.11 Imputation methods
5.11.1 Time-adjusted last observation carried forward (T_LOCF)
Last observed incidence of new DUs carried forward and corrected for the missing time period. This method is based on the assumption of a constant incidence rate of new DUs over time. This T_LOCF value will be calculated in the following way:
• Observed incidence of new DUs = N_d/T_d (where N_d = total number of new DUs observed up to the last assessment, and T_d = treatment day at the last assessment)

• Predicted number of new DUs up to Week 16 = 112 × N_d/T_d (where 16 weeks = 112 days).

5.11.2 Efficacy endpoints

• In case of missing assessments on the number of new DUs, the number of new DUs will be imputed using T_LOCF [Section 5.11.1].

• Patients who had no new DUs observed at the time of premature discontinuation, will be imputed with the worst observed number of new DUs among all completers in the analysis set.

• In case of missing assessments on the number of new DUs at intermediate visits, the number of new DUs will be replaced with the average of the number of new DUs on the closest assessments before and after the missing visit for that individual patient.

5.11.3 Imputation methods for other endpoints

The last available value is carried forward in case of a missing parameter value, unless the patient meets the condition of DU complications [Section 5.4.2]: worst value* replaces the missing value.

* The patient’s worst value at a given visit is his/her baseline value corrected with the highest percentage of worsening from baseline observed during the study, or the worst class index or grade seen in any patient in the relevant analysis.
6 PROCEDURES AND GOOD CLINICAL PRACTICE

6.1 Procedures

6.1.1 Protocol amendments

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or Health Authorities. An amendment could therefore occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by Actelion, and must be reviewed by the Coordinating/Principal Investigator or Steering Committee, as appropriate.

Changes to the Core Patient Information and Informed Consent requested by ECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

6.1.1.1 Non-substantial amendment

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include, but are not limited to, changes in study staff or contact details (e.g., Actelion instead of CRO monitors), or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and Health Authorities (subject to national regulations).

6.1.1.2 Substantial amendment

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of patients, and changes to the objectives or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Patient Information and Informed Consent.

Substantial amendments must be approved by the appropriate ECs/IRBs, and in some jurisdictions by the Health Authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities, and must be signed by the investigators.

6.1.1.3 Urgent amendment

An urgent amendment might become necessary to preserve the safety of the patients included in the study. The requirements for approval must not prevent any immediate action being taken by the investigators or Actelion in the best interests of the patients. If deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases the implementation of urgent
amendments will occur before submission to, and approval by, ECs/IRBs and Health Authorities.

In such cases, the investigator must notify Actelion within 24 hours. A related substantial amendment will be prepared and submitted by Actelion to the appropriate ECs/IRBs and Health Authorities within 10 working days of receiving the notification.

### 6.1.2 Monitoring

The monitor will contact and visit the investigator regularly, and on request must be permitted to have access to all source documents needed to verify the entries on the eCRF and other protocol-related documents, provided that patient confidentiality is maintained in accordance with local regulations. It will be the monitor’s responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the eCRFs. Actelion monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan.

The rules regarding identification of any data recorded directly on the eCRFs and considered to be source data are specified in the Site Guidelines. The investigator must ensure that patient anonymity is maintained. On eCRFs or other documents submitted to Actelion, patients must be identified only by number, and never by name. The investigator must keep a patient identification code list showing the randomization number, the patient’s name, date of birth and address or any other locally accepted identifiers. Documents identifying the patients (e.g., signed informed consent forms) should not be sent to Actelion, and must be kept in strict confidence by the investigator.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator must on request supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In the case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

An initiation visit will be performed before the first patient is included in the study. Monitoring visits and contacts will occur at regular intervals thereafter, according to a
frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

6.1.3 Data management

6.1.3.1 Data collection
Patient Screening and Enrollment data will be completed through the IVRS/IWRS system and eCRF.

Case Report Form data will be captured via electronic data capture (EDC) using the Rave system provided by Medidata Solutions, Inc., a web-based tool. The Investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (ref. to 21 CFR Part 11), and this approval is used to confirm accuracy of the data recorded.

Entries recorded by the patient in the Patient Diary (use of analgesics for DU), HDISS-DU, SHAQ, WPAI-DU, overall hand pain related to digital ulcers, patient-reported global assessment of DU activity completed by the patient, as well as the physician-reported global assessment of DU activity, are considered source data. The study personnel will review and ensure completeness and readability of patient entries.

6.1.3.2 Database management and quality control
Electronic CRFs will be used for all patients. The Investigator will have access to the data throughout the trial life cycle. The eCRF must be kept current to reflect patient status at any time point during the course of the trial.

While entering the data, the Investigator will be prompted by logical checks (error messages) built into the web-base data entry screens performed on the data. Other protocol specific validation programs will run routinely to perform more extensive data checks for accuracy and completeness. Additional data review will be processed in parallel by the Clinical Trial Team, to look for unexpected patterns in data, and other summaries needed for study monitoring. In case problematic data are detected, a query specifying the problem and requesting clarification will be issued and visible via the eCRF by the Investigator, who will then respond and clarify directly onto the eCRF.

This process will continue until database closure.

Laboratory samples will be processed centrally through central laboratory and the results will be sent electronically to Actelion. After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Science Trial Leader and the Trial Statistician.
6.1.4 Recording of data and retention of documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, and the study data to be subsequently verified. These documents are to be classified into two different categories: investigator’s file, and patient clinical source documents.

The investigator’s file will contain the protocol and all protocol amendments, the FDA form 1572 for studies conducted under a US IND (applicable for US sites only), a financial disclosure form, the eCRFs together with all data changes made, EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curricula vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence in accordance with ICH GCP and local regulations.

Patient clinical source documents include, but are not limited to, hospital/clinic records, physicians’ and nurses’ notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc. The Patient Diary, (use of analgesics for DU), HDISS-DU, SHAQ, WPAI-DU, overall hand pain related to digital ulcers, patient-reported global assessment of DU activity completed by the patient, as well as the physician-reported global assessment of DU activity, are considered as source document.

These two categories of documents must be kept on file by the investigator for as long as is necessary to comply with national and international regulations (generally 2 years after either discontinuation of clinical development, or the last marketing approval, of the investigational drug). No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

When source documents are required for the continued care of the patient, appropriate copies should be made for storing off site.

Copies of the electronic CRFs together with all data changes made will be supplied to the investigator at the end of the trial. The Investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

6.1.5 Audit

The Actelion Global Quality Management Department may conduct audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to evaluate compliance with the principles of GCP- and ICH-related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by a Health Authority, the investigator must inform Actelion immediately that such a request has been made.
The investigator must permit such audits by Actelion or Health Authorities, and must facilitate them by providing access to the relevant source documents.

6.1.6 Handling of study drug(s)
Actelion will supply all study drug(s) to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug(s) dispensed to each patient must be available for inspection at any time.

All drug supplies are to be used only in accordance with this protocol, and not for any other purpose. The responsible person must not destroy any drug labels or unused drug supply. On termination of the study, the monitor will collect used and unused patient kits, which will be sent to the warehouse, where the sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers may be destroyed at the site once drug accountability is final and has been checked by the sponsor or its deputy, and written permission for destruction has been obtained from Actelion.

6.1.7 Publication and reporting of study results
Study results will be documented in a clinical study report that will be signed by Actelion representatives and the Coordinating Investigator (or Principal Investigator for single-center studies).

In accordance with standard editorial and ethical practice, the results of Actelion-sponsored studies will be published. Results from multicenter studies must be published or presented at congresses only in their entirety and not as individual center data, except for ancillary studies.

The Coordinating Investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss with the sponsor the interpretation of the study results prior to publication.

Any study-related article or abstract written independently by investigators must be submitted to Actelion for review at least 60 days prior to submission for publication or presentation.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of Actelion, and will be determined by mutual agreement.

6.1.8 Disclosure and confidentiality
By signing this protocol, the investigator agrees to keep all information provided by Actelion in strict confidence, and to request similar confidentiality from his or her staff
and the EC/IRB. Study documents provided by Actelion (including Investigator’s Brochures, protocols, (e)CRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by Actelion to the investigator may not be disclosed to others without direct written authorization from Actelion, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

6.1.9 Premature termination or suspension of the study
Both Actelion and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, Actelion will promptly inform the investigators, the ECs/IRBs and Health Authorities, as appropriate, and provide the reasons for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with Actelion must promptly inform all enrolled patients, and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement from Actelion, the investigator must promptly inform Actelion and the EC/IRB, and must provide Actelion and the EC/IRB with a detailed written explanation of the termination or suspension.

If the EC/IRB terminates or suspends its approval/favorable opinion of a study, the investigator must promptly notify Actelion and provide Actelion with a detailed written explanation of the termination or suspension.

Any premature termination or suspension of the study must be discussed with the DMC and Steering Committee, as appropriate.

6.2 Good Clinical Practice

6.2.1 Ethics and Good Clinical Practice
The investigator will ensure that this study is conducted in full compliance with the principles of the ‘Declaration of Helsinki’ (and its amendments), and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided to each investigational site.

All studies must follow ICH GCP Guidelines and, if applicable, the US Code of Federal Regulations. In other jurisdictions in which GCP Guidelines exist, the investigators will strictly ensure adherence to the stated provisions.

6.2.2 Ethics Committee / Institutional Review Board
The investigator will submit this protocol and any related document provided to the patient (such as patient information used to obtain informed consent) to an EC or IRB.
Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the trial, the documents reviewed, and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations [Section 6.1.1].

### 6.2.3 Informed consent

It is the responsibility of the investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential hazards of the study. The investigator must also explain to the patients that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason. Appropriate forms for documenting informed consent will be provided to the sites prior to the study.

The Informed Consent and Subject Information Leaflet will be provided in the local language.

### 6.2.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the patient in the event of study-related injuries will comply with applicable regulations.
7 REFERENCES


[Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee 1980] Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma


