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✕Initial SAP

Direct mechanical thrombectomy in acute LVO stroke (SKIP study): a randomized controlled trial

Version 1.0

May 2nd, 2016

Statistical Analysis plan

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55 Statistical analysis committee

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60

61 ▪ Methods

62 Patient population

63 Intravenous tissue plasminogen activator-eligible acute ischemic stroke patients
64 with occlusion of the internal cerebral artery or horizontal part of the middle
65 cerebral artery were enrolled into the SKIP study. The occluded vessel was
66 evaluated by magnetic resonance angiography (MRA) or computed tomographic
67 angiography (CTA). Inclusion and exclusion criteria are listed in Table 1.

68

69 Randomization

70 Patients were randomly assigned in a 1:1 ratio to one of two treatment groups
71 using a web-based data management system: the direct MT group or the
72 bridging therapy group. Using a minimization algorithm, we balanced the number
73 of patients into the two treatment groups of each hospital.

74

75 Clinical assessments at 90 days

76 A physician or clinical research coordinator who is blinded to treatment
77 assignment assesses modified Rankin Scale (mRS) at 90 days after onset by
78 telephone interview at 90 days.

79

80 Outcome measures

81 Efficacy and safety end-points in the initial protocol are listed in

82 Supplemental Table 2.

83 The primary outcome measure is the rate of poor outcome defined as

84 mRS 5,6 at 90 days. The secondary outcome measures are shift analysis of the

85 mRS at 90 days after onset, per protocol (PP) analysis of mRS 5,6 at 90 days,

86 and recanalization rate of the occluded arteries. Successful recanalization is

87 defined as an extended modified Thrombolysis in Cerebral Infarction (eTICI)

88 score¹ $\geq 2b$ according to angiographic findings after MT therapy. The safety

89 outcomes are symptomatic ICH defined by the National Institute of Neurological

90 Disorders and Stroke (NINDS)² and Safe Implementation of Thrombolysis in91 Stroke-Monitoring Study (SIT-MOST³) criteria at 36 hours from onset and any

92 ICH, including asymptomatic and symptomatic ICH.

93

94 Sample size calculation95 A previous observational study⁴ showed that poor outcome at 90 days

96 for ischemic stroke was observed in 25% and 47.5% of patients who had

97 received direct MT and bridging therapy, respectively. According to those results,
98 we estimated that 134 patients (67 patients in either group) would need to be
99 enrolled to detect the superiority of direct MT to the combination of IVT and MT,
100 based on a 2-sided α level of 0.05 and a power of 0.80. Accounting for possible
101 treatment failures, protocol violations, and dropouts, we decided to enroll 200
102 patients.

103

104 Statistical analysis

105 The primary study outcome measure is superiority of the favorable
106 outcome at 90 days. We will first use unadjusted logistic regression to test
107 whether direct MT therapy will be superior to bridging therapy.

108 The secondary efficacy analyses include the comparison of ordinal
109 scores on the modified Rankin scale to test for the superiority of the direct MT vs
110 bridging therapy with ordinal logistic regression (shift analysis), where the OR is
111 calculated for each cut-point across the mRS (for example, 0 versus 1–6, then
112 0–1 versus 2–6, and so on), and then a summary OR is calculated from the
113 individual ORs, under the assumption that the individual ORs are the same. We
114 also performed secondary analyses of the primary outcome with adjustment for

115 minimization and key prognostic covariates, as well as secondary analyses in
116 the per-protocol population. Next, clinical characteristics, recanalization success
117 rate, hemorrhagic event rate, and other MT parameters were compared between
118 the two groups using unadjusted logistic regression analysis. The P-values are
119 two-sided. JMP version 11 software (SAS Institute, Cary, NC) was used the
120 analysis.

121

122 Study organization

123 The SKIP study was organized by a central coordinating center located
124 at Nippon Medical School, and conducted in approximately 22 centers in Japan.
125 The SKIP study receives no funding support.

126

127 Supplementary Tables.

128 Table 1. Inclusion and exclusion criteria of the SKIP study

 Inclusion criteria

- Age ≥ 18 and < 86 years at the time of informed consent
 - Clinical diagnosis of acute ischemic stroke with clinical symptoms
 - Modified Rankin scale score ≤ 2
 - ICA or M1 occlusion on MRA or CTA
 - Initial NIHSS ≥ 6
 - ASPECTS on initial DWI ≥ 5 or on initial CT ≥ 6
 - Onset to randomization within 4 h from onset.
 - Written informed consent by patient or next of kin.
-

Exclusion criteria

- Contraindication for contrast agent or endovascular therapy
 - Contraindication for IVT
 - Presence of severe renal disorder (patients undergoing dialysis can be included)
 - Pregnancy or possibility of pregnancy
 - Unlikely to complete the study, such as due to progressive malignant tumor
 - Judged incompatible with the study by the investigators
-

129 ICA, internal carotid artery; ASPECTS: Alberta Stroke Program Early CT Score; M1,
 130 first segment of middle cerebral artery; MRA, magnetic resonance angiography; CTA,
 131 computed tomographic angiography; DWI, diffusion-weighted imaging; IVT, intravenous
 132 thrombolysis

133 Table 2. Efficacy and safety assessment in the initial protocol

 Primary efficacy endpoint

- Poor outcome defined as mRS score 5-6 at 90 days after stroke onset
-

Secondary efficacy endpoints

- The mRS score at 90 days (shift analysis)
 - Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset (non-inferior)
 - Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset (non-inferior)
 - Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset (non-inferior)
 - Improvement of mRS score as of 90 days after stroke onset
 - Recanalization of TICl score 2b or 3 at the end of EVT
 - Recanalization of modified Mori grade 2 or 3 at 72 h after stroke onset
-

Safety endpoints

- ICH on CT or MRI within 36 h after stroke onset.
 - sICH as defined by an increase in NIHSS score of ≥ 4 from baseline on CT or MRI within 36 h after stroke onset.
 - Major bleeding as defined by fatal bleeding, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular or bleeding causing a fall in hemoglobin ≥ 3 g/dL, or leading to transfusion of whole blood or red cells within 24 h
-

after stroke onset

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137 revascularization grading scale and the need for standardization of angiography
138 outcomes in stroke trials. *J Neurointerv Surg* 2014;6:83-6.

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140 1995;333:1581-7.

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147 Artery Anterior Circulation Stroke: A Matched-Pairs Analysis. *Stroke*
148 2016;47:1037-44.

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173 ▪ Statistical analysis committee

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179 ▪ Methods

180 Patient population

181 Intravenous tissue plasminogen activator-eligible acute ischemic stroke patients
182 with occlusion of the internal cerebral artery or horizontal part of the middle
183 cerebral artery are enrolled into the SKIP study. The occluded vessel is
184 evaluated by magnetic resonance angiography (MRA) or computed tomographic
185 angiography (CTA). Inclusion and exclusion criteria are listed in Table 1.

186

187 Clinical assessments at 90 days

188 The mRS is assessed by physical examination or telephone interview at 90 days
189 after onset by a third independent observer, who was also blinded.

190

191 Randomization

192 Patients were randomly assigned in a 1:1 ratio to one of two treatment groups
193 using a web-based data management system: the direct MT group or the
194 bridging therapy group. Using a minimization algorithm, we balanced the number
195 of patients into the two treatment groups of each hospital.

196

197 Outcome measures

198 Efficacy and safety end-points in the initial protocol are listed in Supplemental
199 Table 2. We changed the primary efficacy endpoint from superiority of the rate of
200 poor outcome defined as mRS 5,6 to non-inferiority of the rate of favorable
201 outcome defined as mRS 0-2 on 1 August 2018, because we fit the primary
202 outcome to match other clinical trials of the same theme and change the theme
203 to be useful to clinical practice. the SKIP investigators always requested IRB to
204 use the mRS 0-2 for noninferiority as primary analysis. However the IRB
205 required SKIP investigators to change from mRS 0-2 for noninferiority to mRS
206 5-6 for superiority as primary analysis prior to study start, because there were no
207 confirm data to support the mRS 0-2 than mRS 5-6 approach. Then, when about
208 half the patients had been enrolled in the trial, a group in Germany published an
209 observational study that provided more data regarding the mRS 0-2 endpoint⁴.
210 Therefore, IRB accepted to use mRS 0-2 for noninferiority as primary
211 analysis. We show the end-points in the final protocol in Supplemental Table 3.
212 The primary outcome measure is the rate of favorable outcome defined as
213 modified Rankin scale score of 0-2 at 90 days (noninferiority). The secondary
214 outcome measures are a shift analysis of the modified Rankin scale score at 90

215 days after onset, per protocol (PP) analysis of a modified Rankin scale score of
216 0-2 at 90 days, mortality at 90 days, and reperfusion rate of the occluded arteries.
217 Successful reperfusion is defined as an extended Thrombolysis in Cerebral
218 Infarction (eTICI) score ¹ ≥ 2 (range, 0 [no reperfusion] to 3 [complete
219 reperfusion]) according to digital subtraction angiography findings after
220 mechanical thrombectomy therapy. The safety (adverse) events are
221 symptomatic intracerebral hemorrhage, as defined by the National Institute of
222 Neurological Disorders and Stroke (NINDS ²) and Safe Implementation of
223 Thrombolysis in Stroke-Monitoring Study (SIT-MOST ³) criteria, and any
224 intracerebral hemorrhage including asymptomatic and symptomatic intracerebral
225 hemorrhage at 36 hours from onset.

226

227 Sample size calculation

228 In the initial protocol, we estimated sample size of 134 patients (67
229 patients in either group) for the superiority analysis of poor outcome defined as
230 mRS 5,6 at 90 days. Then, we have changed the primary outcome and thus we
231 re-calculated sample size. A previous observational study⁴ showed that
232 favorable outcome at 90 days for ischemic stroke was observed in 48.6% and

233 35.2% of patients who had received direct MT and bridging therapy, respectively.
234 According to those results, we estimated that 178 patients (89 patients in either
235 group) would need to be enrolled to detect the noninferiority of direct MT to the
236 combination of IVT and MT, based on a 1-sided α level of 0.025 and a power of
237 0.80. Accounting for possible treatment failures, protocol violations, and
238 dropouts, we decided to enroll 200 patients.

239

240 Definition of analysis sets

241 All patients who have been randomised to either control or intervention
242 arms will be included in the full analysis set irrespective of their protocol
243 adherence and continued participation in the study. All analyses will be
244 performed using the full analysis set. Noninferiority analyses of a modified
245 Rankin scale score of 0-2 at 90 days will also be performed using the PP analysis
246 set, which excludes patients whose modified Rankin scale at pre stroke is higher
247 than 2 and a large volume infarct (Alberta Stroke Program Early CT Score of 0-5
248 or DWI- Alberta Stroke Program Early CT Score of 0-4) from full analysis set.

249

250 Statistical analysis

251 The primary study outcome measure is noninferiority of the favorable
252 outcome at 90 days. We will first use unadjusted logistic regression to test
253 whether direct MT therapy will be noninferior to bridging therapy. To satisfy the
254 noninferiority hypothesis, the lower bound of the one-sided 97.5% confidence
255 interval (CI) for the odds ratio (OR) of the primary outcome of the Direct MT
256 group compared with the Bridging group needs to exceed 0.74. This
257 noninferiority margin is derived from a previous meta-analysis of bridging
258 therapy compared with the best medical treatment,⁵ with the margin defined
259 according to the upper bound of the 95% CI for the OR of the primary outcome
260 with standard medical care versus the combination of medical care and MT. The
261 margin of 0.74 represents the midpoint between the upper bound of the 95% CI
262 of the estimated effect of the standard medical care and 1.0 (using bridging
263 therapy with medical care and MT as a reference).

264 In a secondary efficacy analysis, the modified Rankin scale ordinal scores will be
265 compared between groups to test for the non-inferiority of mechanical
266 thrombectomy compared with combined intravenous thrombolysis plus
267 mechanical thrombectomy, using ordinal logistic regression analysis (shift
268 analysis), where the OR will be calculated for each cut-point across the mRS

269 scale score (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and
270 then a summary OR will be calculated from the individual ORs, under the
271 assumption that the individual ORs are the same.. The proportional odds
272 assumption will be validated by a Brant test. We will also performe secondary
273 analyses of the primary outcome with adjustment for minimization and key
274 prognostic covariates, as well as secondary analyses in the PP population.
275 Thereafter, the clinical characteristics, successful reperfusion rate, hemorrhagic
276 events rate, and other mechanical thrombectomy parameters will be compared
277 between the two groups using unadjusted logistic regression analysis. As safety
278 (adverse) events, any and symptomatic intracerebral hemorrhage will be
279 assessed to superiority of mechanical thrombectomy alone compared with
280 combined intravenous thrombolysis plus mechanical thrombectomy.
281 Imputation for missing data will not be conducted because there were no
282 missing data at the time of prespecified, interim safety analysis.
283 Noninferiority analyses use a 1-sided 97.5% CI of the estimated effect whereas
284 other analyses use a 2-sided 95% CI of the estimated effect for judgement of
285 statistical significance. For point estimates, $p < 0.05$ is considered statistically
286 significant. All data analyses are performed with JMP version 11 software (SAS

287 Institute, Cary, NC) and Stata version 14 software (Stata Corp, College Station,

288 TX).

289

290 Study organization

291 In the final protocol, the SKIP study was conducted at 23 stroke centers

292 in Japan. And the SKIP study was funded by the Japanese Society for

293 Neuroendovascular Therapy (JSNET).

294 Supplementary Tables.

295 Table 1. Inclusion and exclusion criteria of the SKIP study

 Inclusion criteria

- Age ≥ 18 and < 86 years at the time of informed consent
 - Clinical diagnosis of acute ischemic stroke with clinical symptoms
 - Modified Rankin scale score ≤ 2
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 - ASPECTS on initial DWI ≥ 5 or on initial CT ≥ 6
 - Onset to randomization within 4 h from onset.
 - Written informed consent by patient or next of kin.
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Exclusion criteria

- Contraindication for contrast agent or endovascular therapy
 - Contraindication for IVT
 - Presence of severe renal disorder (patients undergoing dialysis can be included)
 - Pregnancy or possibility of pregnancy
 - Unlikely to complete the study, such as due to progressive malignant tumor
 - Judged incompatible with the study by the investigators
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296 ICA, internal carotid artery; ASPECTS: Alberta Stroke Program Early CT Score; M1,
 297 first segment of middle cerebral artery; MRA, magnetic resonance angiography; CTA,
 298 computed tomographic angiography; DWI, diffusion-weighted imaging; IVT, intravenous
 299 thrombolysis

300 Table 2. Efficacy and safety assessment in the initial protocol

 Primary efficacy endpoint

- Poor outcome defined as mRS score 5-6 at 90 days after stroke onset
-

Secondary efficacy endpoints

- The mRS score at 90 days (shift analysis)
 - Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset (non-inferior)
 - Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset (non-inferior)
 - Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset (non-inferior)
 - Improvement of mRS score as of 90 days after stroke onset
 - Recanalization of TICl score 2b or 3 at the end of EVT
 - Recanalization of modified Mori grade 2 or 3 at 72 h after stroke onset
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Safety endpoints

- ICH on CT or MRI within 36 h after stroke onset.
 - sICH as defined by an increase in NIHSS score of ≥ 4 from baseline on CT or MRI within 36 h after stroke onset.
 - Major bleeding as defined by fatal bleeding, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular or bleeding causing a fall in hemoglobin ≥ 3 g/dL, or leading to transfusion of whole blood or red cells within 24 h
-

after stroke onset

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302 Table 3. Efficacy and safety assessment in the final protocol

 Primary efficacy endpoint

- Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset

(non-inferior)(intention to treat analysis)

Secondary efficacy endpoints

- The mRS score at 90 days (shift analysis)
 - Poor outcome defined as mRS score 5-6 at 90 days after stroke onset
 - Poor outcome defined as mortality at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset
 - Favorable outcome defined as mRS score 0-1 at 90 days after stroke onset
- (non-inferior)
- Favorable outcome defined as mRS score 0-2 at 90 days after stroke onset
- (non-inferior)(per protocol analysis)
- Favorable outcome defined as mRS score 0-3 at 90 days after stroke onset
- (non-inferior)

- Improvement of mRS score as of 90 days after stroke onset
 - Recanalization of TICl score 2b or 3 at the end of EVT
 - Recanalization of modified Mori grade 2 or 3 at 72 h after stroke onset
-

Safety endpoints

- ICH on CT or MRI within 36 h after stroke onset.
- sICH as defined by an increase in NIHSS score of ≥ 4 from baseline on CT or MRI within 36 h after stroke onset.

- Major bleeding as defined by fatal bleeding, symptomatic bleeding in a critical area or organ, such as intraspinal, intraocular or bleeding causing a fall in hemoglobin ≥ 3 g/dL, or leading to transfusion of whole blood or red cells within 24 h after stroke onset
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306 References

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308 revascularization grading scale and the need for standardization of angiography
309 outcomes in stroke trials. *J Neurointerv Surg* 2014;6:83-6.
- 310 2. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*
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324 ✖A summary of all SAP changes

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Dates of the change	Ver 1.0 change	Ver 2.0 change
8/2/2018	<p><u>Clinical assessments at 90 days</u> A physician or clinical research coordinator who is blinded to treatment assignment assesses modified Rankin Scale (mRS) at 90 days after onset by telephone interview at 90 days.</p>	<p>The modified Rankin scale (mRS) is assessed by physical examination or telephone interview at 90 days after onset by a third independent observer, who was also blinded.</p>
8/2/2018	<p><u>Primary and secondary outcome</u> Efficacy and safety end-points in the initial protocol are listed in Supplemental eTable 2. The primary outcome measure is the rate of poor outcome defined as mRS 5,6 at 90 days. The secondary outcome measures are shift analysis of the mRS at 90 days after onset, per protocol (PP) analysis of mRS 5,6 at 90 days, and recanalization rate of the occluded arteries. Successful recanalization is defined as extendedmodified Thrombolysis in Cerebral Infarction (eTICI) score¹ ≥ 2b according to angiographic findings after MT therapy. The safety outcomes are symptomatic ICH defined by the National Institute of Neurological Disorders and Stroke (NINDS)² and Safe Implementation of Thrombolysis in Stroke-Monitoring Study</p>	<p><u>Primary and secondary outcome</u> Efficacy and safety end-points in the initial protocol are listed in Supplemental eTable 2. We changed the primary efficacy endpoint from superiority of the rate of poor outcome defined as mRS 5,6 to non-inferiority of the rate of favorable outcome defined as mRS 0-2 on 1 August 2018, because we fit the primary outcome to match other clinical trials of the same theme and change the theme to be useful to clinical practice. We show the end-points in the final protocol in Supplemental eTable 3. The primary outcome measure is the rate of favorable outcome defined as modified Rankin scale score of 0-2 at 90 days (noninferiority). The secondary outcome measures are a shift analysis of the modified Rankin</p>

	<p>(SIT-MOST³) criteria at 36 hours from onset and any ICH, including asymptomatic and symptomatic ICH.</p>	<p>scale score at 90 days after onset, per protocol (PP) analysis of a modified Rankin scale score of 0-2 at 90 days, mortality at 90 days, and reperfusion rate of the occluded arteries. Successful reperfusion is defined as an extended Thrombolysis in Cerebral Infarction (eTICI) score¹ ≥ 2 (range, 0 [no reperfusion] to 3 [complete reperfusion]) according to digital subtraction angiography findings after mechanical thrombectomy therapy. The adverse events are symptomatic intracerebral hemorrhage, as defined by the National Institute of Neurological Disorders and Stroke (NINDS²) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SIT-MOST³) criteria, and any intracerebral hemorrhage including asymptomatic and symptomatic intracerebral hemorrhage at 36 hours from onset.</p>
8/2/2018	<p><u>Sample size calculation</u> A previous observational study⁴ showed that poor outcome at 90 days for ischemic stroke was observed in 25% and 47.5% of patients who had received direct MT and bridging</p>	<p><u>Sample size calculation</u> In the initial protocol, we estimated sample size of 134 patients (67 patients in either group) for the superiority analysis of poor outcome defined as mRS 5,6 at 90 days.</p>

	<p>therapy, respectively. According to those results, we estimated that 134 patients (67 patients in either group) would need to be enrolled to detect the superiority of direct MT to the combination of IVT and MT, based on a 2-sided α level of 0.05 and a power of 0.80. Accounting for possible treatment failures, protocol violations, and dropouts, we decided to enroll 200 patients.</p>	<p>Then, we have changed the primary outcome and thus we re-calculated sample size. A previous observational study⁴ showed that favorable outcome at 90 days for ischemic stroke was observed in 48.6% and 35.2% of patients who had received direct MT and bridging therapy, respectively. According to those results, we estimated that 178 patients (89 patients in either group) would need to be enrolled to detect the noninferiority of direct MT to the combination of IVT and MT, based on a 1-sided α level of 0.025 and a power of 0.80. Accounting for possible treatment failures, protocol violations, and dropouts, we decided to enroll 200 patients.</p>
8/2/2018		<p><u>Definition of analysis sets</u> All patients who have been randomised to either control or intervention arms will be included in the full analysis set irrespective of their protocol adherence and continued participation in the study. All analyses will be performed using the full analysis set. Noninferiority analyses of a modified Rankin scale score of 0-2 at 90 days will also be</p>

		<p>performed using the PP analysis set, which excludes patients whose modified Rankin scale at pre stroke is higher than 2 and a large volume infarct (Alberta Stroke Program Early CT Score of 0-5 or DWI- Alberta Stroke Program Early CT Score of 0-4) from full analysis set.</p>
8/2/2018	<p><u>Statistical analysis</u> The primary study outcome measure is superiority of the favorable outcome at 90 days. We will first use unadjusted logistic regression to test whether direct MT therapy will be superior to bridging therapy. The secondary efficacy analyses include the comparison of ordinal scores on the modified Rankin scale to test for the superiority of the direct MT vs bridging therapy with ordinal logistic regression (shift analysis), where the OR is calculated for each cut-point across the mRS (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a summary OR is calculated from the individual ORs, under the assumption that the individual Ors are the same. We also performed secondary analyses of the primary outcome with adjustment for minimization and key prognostic covariates, as</p>	<p><u>Statistical analysis</u> The primary study outcome measure is noninferiority of the favorable outcome at 90 days. We will first use unadjusted logistic regression to test whether direct MT therapy will be noninferior to bridging therapy. To satisfy the noninferiority hypothesis, the lower bound of the one-sided 97.5% confidence interval (CI) for the odds ratio (OR) of the primary outcome of the Direct MT group compared with the Bridging group needs to exceed 0.74. This noninferiority margin is derived from a previous meta-analysis of bridging therapy compared with the best medical treatment,⁵ with the margin defined according to the upper bound of the 95% CI for the OR of the primary outcome with standard medical care versus the combination of</p>

	<p>well as secondary analyses in the per-protocol population. Next, clinical characteristics, recanalization success rate, hemorrhagic event rate, and other MT parameters were compared between the two groups using unadjusted logistic regression analysis. The P-values are two-sided. JMP version 11 software (SAS Institute, Cary, NC) was used for the analysis.</p>	<p>medical care and MT. The margin of 0.74 represents the midpoint between the upper bound of the 95% CI of the estimated effect of the standard medical care and 1.0 (using bridging therapy with medical care and MT as a reference). In a secondary efficacy analysis, the modified Rankin scale ordinal scores will be compared between groups to test for the non-inferiority of mechanical thrombectomy compared with combined intravenous thrombolysis plus mechanical thrombectomy, using ordinal logistic regression analysis (shift analysis), where the OR will be calculated for each cut-point across the mRS scale score (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a summary OR will be calculated from the individual ORs, under the assumption that the individual ORs are the same. The proportional odds assumption will be validated by a Brant test. We will also perform secondary analyses of the primary outcome with adjustment for minimization and key prognostic covariates, as well as secondary analyses in the PP population. Thereafter,</p>
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		<p>the clinical characteristics, successful reperfusion rate, hemorrhagic events rate, and other mechanical thrombectomy parameters will be compared between the two groups using unadjusted logistic regression analysis. As safety (adverse) events, any and symptomatic intracerebral hemorrhage will be assessed to superiority of mechanical thrombectomy alone compared with combined intravenous thrombolysis plus mechanical thrombectomy. Imputation for missing data will not be conducted because there were no missing data at the time of prespecified, interim safety analysis.</p> <p>Noninferiority analyses use a 1-sided 97.5% CI of the estimated effect whereas other analyses use a 2-sided 95% CI of the estimated effect for judgement of statistical significance. For point estimates, $p < 0.05$ is considered statistically significant. All data analyses are performed with JMP version 11 software (SAS Institute, Cary, NC) and Stata version 14 software (Stata Corp, College Station, TX).</p>
8/2/2018	<u>Study organization</u>	<u>Study organization</u>

	<p>The SKIP study was organized by a central coordinating center located at Nippon Medical School, and conducted in approximately 22 centers in Japan. The SKIP study receives no funding support.</p>	<p>In the final protocol, the SKIP study was conducted at 23 stroke centers in Japan. And the SKIP study was funded by the Japanese Society for Neuroendovascular Therapy (JSNET).</p>
8/2/2018	<p>References</p> <ol style="list-style-type: none"> 1.Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. J Neurointerv Surg 2014;6:83-6. 2.Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7. 3.Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82. 4.Broeg-Morvay A, Mordasini P, Bernasconi C, et al. Direct Mechanical Intervention Versus Combined Intravenous and Mechanical Intervention in Large Artery Anterior Circulation Stroke: A Matched-Pairs Analysis. Stroke 2016;47:1037-44. 	<p>References</p> <ol style="list-style-type: none"> 1.Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. J Neurointerv Surg 2014;6:83-6. 2.Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7. 3.Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82. 4.Weber R, Nordmeyer H, Hadisurya J, et al. Comparison of outcome and interventional complication rate in patients with acute stroke treated with mechanical thrombectomy with and without bridging thrombolysis. J Neurointerv Surg 2017;9:229-33. 5.Goyal M, Menon BK, van

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