

1 **China Angioplasty & Stenting for Symptomatic Intracranial Severe**
2 **Stenosis (CASSISS)**

3
4 **A prospective multi-center, randomized controlled trial (RCT)**
5

6 **Statistical Analysis**
7 **Plan**

8
9 **Ver. 1.0**

10 **Version date: May 10, 2015**
11

Type of research: Investigator-initiated
Phase IV clinical trial
Organizer: Xuanwu Hospital
Capital Medical University
Statistical analysis: Clinical Research Institute
Peking University

12
13 **Author: _____**

14 **Date: _____**

15 **Haibo Wang**

16 **Clinical Research Institute of Peking University**
17

18

CONTENTS

19	1. ABBREVIATIONS	5
20	2. PROTOCOL ABSTRACT.....	7
21	2.1 STUDY PURPOSE	7
22	2.2 STUDY DESIGN.....	7
23	2.3 SAMPLE SIZE	7
24	2.4 BLINDING AND RANDOMIZATION	8
25	2.5 INTERVENTIONS	8
26	2.6 STUDY POPULATION AND DIAGNOSTIC CRITERIA.....	9
27	2.6.1 Inclusion criteria.....	9
28	2.6.2 Exclusion criteria	10
29	3. ASSESSMENT OF OUTCOME EVALUATION.....	14
30	3.1 OUTCOME EVALUATION.....	14
31	3.1.1 <i>Primary Outcome</i>	14
32	3.1.2 <i>Secondary Outcomes</i>	14
33	3.2 SAFETY OUTCOMES.....	14
34	4. DATA SAFETY MONITORING BOARD (DSMB).....	16
35	5. ANALYSIS DATA SET.....	17
36	6. PROCESSING OF MISSING DATA	18
37	7. STATISTICAL ANALYSIS METHOD.....	19
38	7.1 GENERAL PRINCIPLES OF STATISTICAL ANALYSIS	19
39	7.2 ANALYSIS PLAN	19
40	7.3 COMPLETION	20
41	7.4 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS	20
42	7.5 EFFICACY ANALYSIS.....	20
43	7.5.1 Main Efficacy index.....	20
44	7.5.2 Secodary Efficacy index.....	21
45	7.5.3 <i>Others</i>	21
46	7.6 SAFETY ANALYSIS	22
47	8. STATISTICAL ANALYSIS RESULTS.....	23
48	8.1 DISTRIBUTION OF INCLUDED PATIENTS	23
49	8.2 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS	26
50	8.3 EFFICACY EVALUATION	32
51	8.3.1 <i>Primary efficacy outcome</i>	32
52	8.3.2 Secondary efficacy outcomes.....	33

53	8.4 SAFETY ANALYSIS	42
54	8.4.1 ADVERSE EVENTS.....	42
55		
56		

57

APPENDIX

58 TABLE 1 POPULATION DISTRIBUTION OF EACH CENTER..... 23

59 TABLE 2 LIST OF PATIENTS NOT INCLUDED IN THE FAS/PPS SET..... 24

60 TABLE 3 DATA SETS OF ENROLLED PATIENTS AND SAFETY AND EFFICACY ANALYSIS SETS.

61 24

62 TABLE 4 DEMOGRAPHIC DATA 26

63 TABLE 5 BASELINE INFORMATION 26

64 TABLE 6 PAST MEDICAL HISTORY 28

65 TABLE 7 HISTORY OF PREVIOUS AND CURRENT MEDICAL THERAPY FOR

66 CEREBROVASCULAR DISEASES 29

67 TABLE 8 MEDICAL RECORDS OF THE PRESENT ISCHEMIC ATTACK..... 29

68 TABLE 9 INCIDENCE OF PRIMARY OUTCOME (STROKE OR DEATH) 12 MONTHS AFTER

69 RANDOMIZATION 32

70 TABLE 10 INCIDENCE OF DISABLING STROKE OR DEATH WITHIN 36 MONTHS AFTER

71 RANDOMIZATION 33

72 TABLE 11 2-YEAR RATE OF THE SAME-TERRITORY STROKE..... 35

73 TABLE 12 3-YEAR RATE OF THE SAME-TERRITORY STROKE 36

74 TABLE 13 CHANGES OF NEUROLOGICAL FUNCTION EVALUATION (MRS AND NIHSS SCORE)

75 38

76 TABLE 14 ANY STROKE, SEVERE TIA, CARDIOVASCULAR EVENTS RELATED TO STENTING OR

77 MEDICAL THERAPY WITHIN A FOLLOW-UP OF 3 YEARS 41

78 TABLE 15 SUMMARY OF ADVERSE EVENTS 42

79 TABLE 16 SUMMARY OF THE SEVERITY OF ADVERSE EVENTS..... 43

80

82 **1. Abbreviations**

ALT	Serum alanine aminotransferase
AST	Serum glutamic-oxalacetic transaminase
APTT	Activated partial thromboplastin time
BUN	Urea nitrogen (blood)
BMI	Body mass index
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
CTA	Computed tomography angiography
CTP	CT perfusion scan
DSA	Digital subtraction angiography
DSMB	Data Safety Monitoring Board
DWI	Magnetic resonance diffusion weighted imaging
EC	Ethics committee
ECG	Electrocardiogram
FAS	Full analysis set
FBS	Fasting plasma glucose
HDL-C	High density lipoprotein cholesterol
ICF	Informed consent
INR	International standard ratio
ITT	Intention to treat
LDL-C	Low density lipoprotein cholesterol
LOCF	The last observation was carried forward
MCA	Middle cerebral artery
MedDRA	Dictionary of medical terms used for drug registration

MRA	Nuclear magnetic angiography
mRS	Modified Rankin Scale
MTT	Mean transit time
NIHSS	National Institutes of Health Stroke Assessment Scale
PET	Positron emission tomography
PPS	Per-protocol set
PT	Prothrombin time
PWI	Perfusion-weighted imaging
RCT	Randomized controlled trial
SFDA	State Food and Drug Administration
TCD	Transcranial Doppler scan
TIA	Transient ischemic attack
XeCT	Xenon enhanced computed tomography

83

84

85 **2. Protocol Abstract**

86 **2.1 Study purpose**

87 Main purpose: to determine whether PTAS (using the Gateway PTA balloon catheter
88 and Wingspan Stent System, Stryker, Fremont, CA, USA) combined with medical
89 therapy is superior to medical therapy alone for preventing the primary outcome
90 (stroke or death within 30 days after enrollment, or stroke in the territory of the
91 symptomatic intracranial artery between 30 days through 1 year in patients with
92 recent TIA or non-disabling stroke caused by 70% to 99% stenosis of a major
93 intracranial artery).

94

95 Secondary purpose: to compare outcomes between groups in terms of:

96 ☞ Disabling stroke or death after enrollment through 3 years in both arms;

97 ☞ 2-year rate of the same-territory stroke;

98 ☞ 3-year rate of the same-territory stroke;

99 ☞ Any stroke, TIA, or cardiovascular events within a follow-up of 3 years;

100 ☞ Death rate in both arms within a follow-up of 3 years;

101 ☞ mRS, NIHSS scores of patients.

102

103 **2.2 Study design**

104 This study is a multicenter, randomized, open-label, outcome-blinded trial comparing
105 medical therapy alone or medical therapy plus stenting with the use of the Wingspan
106 Stent system in patients with transient ischemic attack (TIA) or non-disabling
107 ischemic stroke caused by 70%-99% stenosis of a major intracranial artery.

108

109 **2.3 Sample size**

110 For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of
111 ipsilateral stroke risk in medical therapy group WASID study was 18%, which was

112 7.3% in a study by the Wingspan stent therapy (Wei-jian Jiang, etc.). At a significance
113 level of 5% on both sides, the absolute difference of 10.7% (relative risk reduction:
114 59%), and a power of 80%, within 12 months of follow-up, a total of 302 patients
115 needs to be evaluated. Assuming a 20% incidence of loss of follow-up and/or
116 withdrawal, a total of 380 patients, 190 per group, are required to be enrolled in this
117 study.

118

119 **2.4 Blinding and randomization**

120 Complete randomization methodology will be used. Once the patient meets the
121 inclusion criteria after signing the informed consent form, the researcher will
122 immediately make a phone call to the research group, and the answering staff will
123 assign the patient a random number according to the patient number, and the random
124 number will associate the patient with the corresponding treatment group. Patients
125 will be given medical therapy alone or Wingspan stent plus medical therapy,
126 depending on the treatment group randomly assigned. Patients randomly assigned to
127 the medical treatment group will be discharged after DSA examination.

128 This study is an open, outcome-blinded study.

129

130 **2.5 Interventions**

131 Medical therapy:

132 Medical therapy will be identical in both arms and will be similar to the previously
133 described risk factor management for the SAMMPRIS trial. In brief, aspirin 100 mg
134 plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75 mg
135 alone per day thereafter) and management of risk factors. Medical management of
136 risk factors consists of control of low-density lipoprotein (LDL-C) (target:
137 LDL-C<2.58mmol/L (100 mg/dL) with statins, and hypertension (systolic pressure
138 <140 mmHg [<130mmHg in the case of patients with diabetes] and diastolic pressure
139 <90 mmHg) based on 2014 AHA/ASA guidelines.

140

141 Stenting:

142 Patients randomized to stenting will be scheduled for intervention within three to five
143 business days. The study protocol requires that the stenting procedure be performed
144 under general anesthesia by a qualified operator at each site. Intensive management
145 of risk factors will be applied thereafter.

146

147 **2.6 Study population and diagnostic criteria**

148 This trial aims to recruit patients who have had a TIA or ischemic stroke ($mRS \leq 2$) and
149 advanced ICAS (70%–99% on angiogram). Catheter angiography is required to
150 confirm 70%–99% stenosis by the WASID criterion for a patient to qualify. Patients
151 who have an ischemic stroke within the last three weeks will not be included because
152 of concern for hemorrhagic transformation.

153

154 **2.6.1 Inclusion criteria**

155 Detailed inclusion criteria were as follows:

156 1. Eligible patients aged between 30 and 80 years; intracranial arterial stenosis
157 related to the following non-atherosclerotic factors will be not be considered:
158 arterial dissection, moya-moya disease; vasculitic disease; herpes zoster,
159 varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial
160 infection; any intracranial stenosis associated with cerebrospinal fluid pleocytosis;
161 radiation-induced vasculopathy; fibromuscular dysplasia; sickle cell disease;
162 neurofibromatosis; benign angiopathy of central nervous system; postpartum
163 angiopathy; suspected vasospastic process, and suspected recanalized
164 embolus;

165 2. Symptomatic intracranial stenosis: presented with transient ischemic stroke (TIA)
166 or stroke within the past 12 months attributed to 70%-99% stenosis of a major
167 intracranial artery (ICA, MCA [M1], vertebral artery, or basilar artery [BA]);

- 168 3. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by catheter
169 angiography for enrollment in the trial;
- 170 4. Remote infarctions on MRI scan, which can be accounted for by the occlusion of
171 the terminal cortical branches or hemodynamic compromise (perforator occlusion
172 excluded). Infarction due to perforators occlusion is defined as basal ganglia or
173 brainstem/thalamus infarction related with M1 or BA stenosis;
- 174 5. Expected ability to deliver the stent to the lesion;
- 175 6. All the patients should be performed with stenting beyond a duration of three
176 weeks from the latest ischemic symptom onset;
- 177 7. No recent infarctions identified on MRI (indicated as high signals on DWI series)
178 upon enrollment;
- 179 8. No massive cerebral infarction (>1/2 MCA territory), intracranial hemorrhage,
180 epidural or sub-dural hemorrhage, and intracranial brain tumor on CT or MRI
181 scan;
- 182 9. mRS scale score of ≤ 2 ;
- 183 10. Target vessel reference diameter must be measured to be 2.00 mm to 4.50 mm;
184 target area of stenosis is ≤ 14 mm in length;
- 185 11. No childbearing potential or has a negative pregnancy test within the past one
186 week prior to study procedure; female patients had normal menses in the last 18
187 months;
- 188 12. Patient is willing and able to return for all follow-up visits required by the protocol;
- 189 13. Patients understand the purpose and requirements of the study and have signed
190 informed consent form.

191

192 **2.6.2 Exclusion criteria**

193 Detailed exclusion criteria were as follows:

- 194 1. Refractory to general anesthesia; not able to be overcome by pre-treatment with
195 medical therapy
- 196 2. Any condition that precludes proper angiographic assessment
- 197 3. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is
198 proximal or distal to the target intracranial lesion
- 199 4. Bilateral intracranial VA stenosis of 70%–99% and uncertainty about which lesion
200 is symptomatic (for example, if patient has pon, midbrain, temporal and occipital
201 symptoms)
- 202 5. Presence of a previously placed intravascular stent or graft in the ipsilateral
203 distribution within 30 days
- 204 6. Previous treatment of target lesion with a stent, angioplasty, or other mechanical
205 device, or plan to perform staged angioplasty followed by stenting of target lesion
- 206 7. Severe vascular tortuosity or anatomy that would preclude the safe introduction of
207 a guiding catheter, guiding sheath or stent placement
- 208 8. Plan to perform concomitant angioplasty or stenting of an extracranial vessel
209 tandem to an ipsilateral intracranial stenosis
- 210 9. Presence of intraluminal thrombus proximal to or at the target lesion
- 211 10. Any aneurysm proximal to or distal to intracranial stenotic artery
- 212 11. Intracranial tumors or any intracranial vascular malformations
- 213 12. Computed tomographic or angiographic evidence of severe calcification at target
214 lesion
- 215 13. Thrombolytic therapy within 24 hours before enrollment
- 216 14. Evolving stroke or progressive neurologic signs within 24 hours before enrollment
- 217 15. Stroke of sufficient size (>5 cm on CT or MRI) to place patient at risk of
218 hemorrhagic transformation during the procedure; hemorrhagic transformation of
219 an ischemic stroke within the past 15 days

-
- 220 16. Previous spontaneous intracerebral (parenchymal) or other intracranial
221 (subarachnoid, subdural, or epidural) hemorrhage within 30 days
- 222 17. Untreated chronic subdural hematoma >5 mm in thickness
- 223 18. Other cardiac sources of emboli such as left ventricular aneurysms, intracardiac
224 filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcified
225 aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal
226 aneurysm, left atrial myxoma
- 227 19. Myocardial infarction within previous 30 days
- 228 20. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the
229 past six months, or history of paroxysmal atrial fibrillation requiring chronic
230 anticoagulation
- 231 21. Intolerance or allergic reaction to any of the medical therapy, including aspirin,
232 clopidogrel, heparin, and local or general anesthetics
- 233 22. History of life-threatening allergy to contrast medium. If not life threatening and
234 can be effectively pre-treated, patient can be enrolled at physicians' discretion
- 235 23. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
- 236 24. Active bleeding diathesis or coagulopathy; active peptic ulcer disease, major
237 systemic hemorrhage within 30 days, active bleeding diathesis, platelets count
238 <125,000, hematocrit <30, Hgb <10 g/dl, uncorrected INR >1.5, bleeding time >1
239 minute beyond upper limit normal, or heparin-associated thrombocytopenia that
240 increases the risk of bleeding, uncontrolled severe hypertension (systolic
241 BP>180mm hg or diastolic BP>115mm hg), severe liver impairment (AST or 25.
242 ALT >3 times normal, cirrhosis), creatinine >265.2 mmol/l (unless on dialysis).
243 Major surgery (including open femoral, aortic, or carotid surgery) within previous
244 30 days or planned in the next 90 days after enrollment
- 245 25. Indication for warfarin or heparin beyond enrollment (exceptions allowed for use
246 of systemic heparin during stenting procedure or subcutaneous heparin for deep
247 venous thrombosis prophylaxis while hospitalized)

248 26. Inability to understand and cooperate with study procedures or sign informed
249 consent

250 27. Severe dementia or psychiatric problems that prevent the patients from following
251 an outpatient program reliably

252 28. Pregnancy or of childbearing potential and unwilling to use contraception for the
253 duration of this study

254 29. Actively participating in another drug or device trial that has not completed the
255 required protocol follow-up period

256

257 **3. Assessment of Outcome evaluation**

258 **3.1 Outcome evaluation**

259 3.1.1 Primary Outcome

260 Stroke or death within 30 days after enrollment or stroke in the territory of qualifying
261 artery (SIT) beyond 30 days through 1 year.

262

263 3.1.2 Secondary Outcomes

264 ☞ Disabling stroke or death within 3 years after randomization;

265 ☞ 2-year rate of SIT;

266 ☞ 3-year rate of SIT;

267 ☞ Death rate within 3 years;

268 ☞ Any stroke, TIA, or cardiovascular events within 3 years.

269

270 **Note**

271 Stroke is defined as the rapid loss of brain function due to disturbance in the blood
272 supply to the brain that persists beyond 24 hours. This can be due to ischemia or
273 hemorrhage.

274

275 TIA is defined as rapidly developed clinical signs of focal or global disturbance of
276 cerebral function lasting longer than 10 minutes but fewer than 24 hours, with no
277 apparent nonvascular cause.

278

279 **3.2 Safety outcomes**

280 Investigators should take appropriate treatment for AEs to ensure the safety of
281 patients and track all AEs/SAEs until they are properly resolved, or the condition is
282 stable. Additional medical procedures and/or referral to a medical specialist may be

283 required to confirm whether the patients are qualified to continue to participate in the
284 study.

285

286 **4. Data Safety Monitoring Board (DSMB)**

287 An independent data safety monitoring committee composed of experts in
288 neurosurgery, internal medicine, neuroradiology, and biostatistics who are not
289 involved in the study is responsible for the following:

290 1. All potential outcome events including TIA, stroke, and death will be reviewed and
291 confirmed. Clinical records and imaging results related to any outcomes are required
292 to be emailed to the outcome committee, and the outcome committee's decision will
293 be the final decision.

294 2. Efficacy and safety data, as well as balance of patient benefits and risks will be
295 reviewed regularly. Timely recommendations will be given to the executive committee
296 on whether to continue, modify, or discontinue the study.

297

298 **5. Analysis data set**

299 Full Analysis Set (FAS): all the subjects who are randomized into groups will be
300 included, except the subjects who do not meet the inclusion and exclusion criteria and
301 who are withdrawn immediately after randomization without receiving any intervention
302 will be excluded. According to the intention-to-treat (ITT) principle, all randomized
303 patients will be analyzed according to the treatment group assigned to them at the
304 time of randomization.

305

306 Per-protocol Set (PPS): All patients who are treated according to the study protocol
307 (the eligibility criteria, the assigned treatment after randomization, additional
308 medication protocol, the follow-up protocol, and completion of the case report form).

309

310 Safety Analysis Set (SAS): Randomized patients who receive at least one dose of
311 antiplatelet therapy with a documented safety outcome.

312

313 Efficacy analysis will be carried out based on the FAS and the PPS, and the
314 conclusions will be made based on the FAS. All baseline demographic data analyses
315 will be performed on the basis of the FAS and safety assessments will be performed
316 on the SAS.

317

318 **6. Processing of missing data**

319 For patients who die or are lost to follow-up within 36 months after randomization, the
320 30-day, 12-month, and 36-month NIHSS and mRS score will be filled using the last
321 observed value (LOCF) method. For other missing data, no filling or other processing
322 will be conducted. For survival analysis, missing data will be considered as censored.
323

324 **7. Statistical analysis method**

325 **7.1 General principles of statistical analysis**

326 Prior to database locking, the statistician is responsible for developing a statistical
327 analysis plan in consultation with the principal investigator. SAS 9.4 statistical
328 software will be used. The efficacy evaluation includes the analysis of PPS and FAS
329 sets, and the conclusion will be based on the FAS set. SAS set analysis will be used
330 for safety evaluation.

331

332 All statistical tests will be conducted using a two-sided test, and a p-value of 0.05 or
333 less will be considered statistically significant (unless otherwise specified).

334 For patients who cross groups, that is, the actual group is not consistent with the
335 randomly assigned group, efficacy will be analyzed according to the ITT principle
336 based on the FAS, and safety will be analyzed according to the SAS.

337

338 **7.2 Analysis plan**

339 After the study protocol is finalized, the statistician will develop the statistical analysis
340 plan in consultation with the principal investigator. All the analyses will be performed
341 with the use of SAS software, version 9.4 (SAS Institute, license number: 11202165).

342

343 Numerical variables will be presented with mean, standard deviation (normally
344 distributed), or median (interquartile interval). Categorical and hierarchical variables
345 will be presented with the number of cases and percentages.

346

347 Appropriate method for comparison of baseline between two groups will be adopted
348 according to the types of variables, and the comparison of numerical variables will be
349 tested with t-test (normal distribution) or Wilcoxon rank test according to the data
350 distribution, categorical variables with chi-square test or the exact probability method

351 (if a chi-square test is not applicable), hierarchical data with Wilcoxon rank test or
352 CMH.

353 **7.3 Completion**

354 The number of patients enrolled in each center, the number of patients who complete
355 the trial and the number of patients withdrawn from the trial will be summarized, and
356 the list of patients not included in the FAS/PPS set and the reasons for exclusion will
357 be listed. The number of cases in each group FAS/PPS dataset, the distribution of
358 cases in each center, and a detailed list of incomplete causes will be listed.

359

360 **7.4 Demographic data and baseline characteristics**

361 Baseline data such as patient demographic characteristics (age and gender), vital
362 signs, past medical history, treatment history and current medical history will be
363 described, and baseline data such as age, gender and BMI of the two groups will be
364 compared to measure the comparability of the two groups.

365

366 **7.5 Efficacy analysis**

367 FAS and PPS will be used for efficacy analysis.

368 **7.5.1 Main Efficacy index**

369 Stroke or death within 30 days after randomization; And stroke in the territory of
370 qualifying artery (SIT) beyond 30 days through 12 months after randomization.

371

372 The incidence of stroke or death at 12 months will be compared between the medical
373 therapy group and the stent group, and a 95% confidence interval will be calculated
374 for the difference between the two groups. CMH Chi-square test considering
375 multicenter design will be adopted for inter-group comparison. If the impact of other

376 factors is adjusted, Logistics regression model can be considered for inter-group
377 comparison.

378

379 The Log Rank test will be used to analyze the primary efficacy outcomes, and the
380 center information will be stratified as covariates. The Cox proportional risk model will
381 be used to calculate HR and its 95% confidence interval (CI) to estimate efficacy. The
382 model included the same covariates as the Log Rank test for fitting. Kaplan-Meier
383 curves will be plotted by treatment group.

384

385 For comparison of patient demographic characteristics (age, gender), vital signs,
386 medical history, history of treatment and the medical records of baseline data
387 between groups, if there are important significant differences for baseline data, the
388 Cox proportional hazards model will be used for adjustment of these baseline
389 variables, which will be included as a sensitivity analysis.

390

391 **7.5.2 Secodary Efficacy index**

392 Disabling stroke or death after enrollment within 3 years in both arms; 2) 2-year rate
393 of SIT; 3) 3-year rate of SIT; 4) any stroke, TIA, or cardiovascular events within 3
394 years; 5) survival rate within 3 years. All above will be analyzed using the same
395 method as the primary efficacy outcomes. The incidence of each outcome and the
396 95% confidence interval will be described by groups.

397

398 **7.5.3 Others**

399 Mixed effects model will be used to compare the changes of neurological function
400 indexes between groups. At the same time, the dichotomous variables will be
401 transformed by selecting clinically significant cut-off points for inter-group
402 comparison. For mRS, 0-2 versus 3-6 will be used. For NIHSS, an increase of 4
403 points or more from baseline to 12 months will be considered to have deteriorated
404 neurological function. CMH Chi-square test considering multicenter design will be

405 adopted for inter-group comparison. If other factors are adjusted, Logistics regression
406 model can be considered for inter-group comparison.

407 **7.6 Safety analysis**

408 The safety evaluation will be analyzed on the SAS dataset.

409 The number of adverse events of the two groups, as well as the incidence of adverse
410 events, serious adverse events will be described in tables. The changes of laboratory
411 and ECG will be described in tables. Procedure-related complications within 30 days
412 after operation in the stent group will be analyzed. Chi-square test/Fisher exact test
413 will be used to compare the incidence of adverse events and the incidence of serious
414 adverse events between the two groups.

415

416 **8. Statistical analysis results**

417 **8.1 Distribution of included patients**

418 Table 1 Population distribution of each center1

	FAS			PPS			SS (Actual Group)		
Center	PTAS group	Medical group	Total	PTAS group	Medical group	Total	PTAS group	Medical group	Total
Total number									

419

420

421

422 Table 2 List of patients not included in the FAS/PPS set2

Center	Patient ID	Time of enrollment	Reason of exclusion	Included in analysis dataset		
				PPS	FAS	SS

423

424 Table 3 Data sets of enrolled patients and safety and efficacy analysis sets.3

	Items	PTAS group	Medical group	Total
The whole data set				
	Randomly enrollment			
Not included in the FAS set				
	Failure to meet inclusion/exclusion criteria			
	Exit after randomization			
Suspension during study				
	Upon requests from subjects or subject's legal authorized representatives.			
	lost of follow-up			
	Crossover			
	Failure to follow the plan			
	Other			
Safety analysis set				
	SS (Actual Group)			
Efficacy analysis set				

	FAS			
	PPS			

425

426

427 **8.2 Demographic data and baseline characteristics**

428 Table 4 Demographic data4

Items	Indicators	Total	PTAS group	Medical group	P
Age (years)	Mean (SD)				
Gender	Male, n (%)				
	Female, n (%)				
Ethnicity	Han, n (%)				
	Other, n (%)				

429

430

431 Table 5 Baseline information5

Items	Indicators	Total	PTAS group	Medical group	P
Systolic blood pressure (mmHg)	Mean (SD)				
Diastolic blood pressure (mmHg)	Mean (SD)				
Heart rate (times per minute)	Mean (SD)				
BMI (kg/m ²)	Mean (SD)				
Smoking history	None n (%)				

Items	Indicators	Total	PTAS group	Medical group	P
	Previous n (%)				
	Current n (%)				
Alcohol use	No n (%)				
	Previous n (%)				
	Current n (%)				
Family history of cerebrovascular disease	No n (%)				
	Yes n (%)				
Family history of cardiovascular disease	No n (%)				
	Yes n (%)				
High density lipoprotein cholesterol	Mean (SD)				
Low density lipoprotein cholesterol	Mean (SD)				
Total cholesterol	Mean (SD)				
triglycerides	Mean (SD)				
C-reactive protein	Mean (SD)				
HbA1c	Mean (SD)				

433

 434 Table 6 Past medical history⁶

Items	Indicators	Total	PTAS group	Medical group	P
Hypertension	No n (%)				
	Yes n (%)				
Diabetes	No n (%)				
	Yes n (%)				
Hyperlipidemia	No n (%)				
	Yes n (%)				
Coronary heart disease (CHD)	No n (%)				
	Yes n (%)				
Myocardial infarction	No n (%)				
	Yes n (%)				
Atrial fibrillation	No n (%)				
	Yes n (%)				
Peripheral vascular disease	No n (%)				
	Yes n (%)				
Alimentary ulcer	No n (%)				
	Yes n (%)				

435

436

437 Table 7 History of previous and current medical therapy for cerebrovascular diseases7

Items	Indicators	Total	PTAS group	Medical group	P
Antiplatelet agent	No n (%)				
	Yes n (%)				
Anticoagulant drugs	No n (%)				
	Yes n (%)				
History of radiotherapy for cerebrovascular disease	No n (%)				
	Yes n (%)				
History of surgical treatment of cerebrovascular disease	No n (%)				
	Yes n (%)				

438

439

440 Table 8 Medical records of the present ischemic attack.8

Items	Indicators	Total	PTAS group	Medical group	P
-------	------------	-------	------------	---------------	---

Items	Indicators	Total	PTAS group	Medical group	P
Ischemia-cerebrovascular disease occurred within 12 months	Cerebral infarction n (%)				
	TIA n (%)				
Time from symptom onset to randomization	Median (IntQ)				
Artery stenosis	Intracranial segment of internal carotid artery N (%)				
	Middle cerebral artery N (%)				
	Intracranial segment of vertebral artery N (%)				
	Basilar artery N (%)				
	Others n (%)				
Stenosis degree	Median (IntQ)				
	70-79% n (%)				
	80-89% n (%)				
	90-99% n (%)				
Mori classification	Short of n (%)				

Items	Indicators	Total	PTAS group	Medical group	P
	Tubular n (%)				
	Dispersion of n (%)				
mRS score	Median (IntQ)				
NIHSS score	Median (IntQ)				

441

442

443 **8.3 Efficacy evaluation**

444 8.3.1 Primary efficacy outcome

445 Table 9 Incidence of primary outcome (stroke or death) 12 months after randomization9

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Stroke or death	or No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95% CI				
	Testing statistic (CMH)				
	P value				
	Outcome Event (%)				
	Loss (%)				
	Incidence				
	95%CI				
	Log - rank test				
	P values				

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Cox regression	Hazard Ratio				
	95% CI				
	P values				
Cox regression (sensitivity analysis)	Hazard Ratio				
	95%CI				
	P values				

446 Note: Cox regression adjusted for variables

447

448 Figure 1 Incidence of primary outcome (stroke or death) within 12 months after randomization (KM curve) (FAS)1

449

450 Figure 2 Incidence of primary end point (stroke or death) within 12 months after randomization (KM curve) (PPS)2

451

452

453 **8.3.2 Secondary efficacy outcomes**

454 Table 10 Incidence of disabling stroke or death within 36 months after randomization10

Items	Indications	FAS		PPS		
		PTAS group	Medical group	PTAS group	Medical group	
Disabling stroke or death	No n (%)					
	Yes n (%)					
	N (Missing)					
	Difference of inter-group rate 95%CI					
	Test statistics (CMH)					
	P values					
	Outcome Event (%)					
	Loss (%)					
	Median event time					
	95% CI					
	Log - rank test					
	P values					
	Cox regression	Hazard Ratio				
		95%CI				
P values						

455 Note: Cox regression adjusted for variables

456

457 Figure 3 Disabling stroke or death within 36 months after randomization (KM curve) (FAS)3

458

459 Figure 4 Disabling stroke or death within 36 months after randomization (KM curve) (PPS)4

460

461

462

463 Table 11 2-year rate of the same-territory stroke11

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				

Items	Indications	FAS	Medical group	PPS	Medical group
		PTAS group		PTAS group	
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

464 Note: Cox regression adjusted for variables

465

466 Figure 5 2-year rate of the same-territory stroke (KM curve) (FAS)5

467

468 Figure 6 2-year rate of the same-territory stroke (KM curve) (PPS)6

469

470

471 Table 12 3-year rate of the same-territory stroke 12

Items	Indications	FAS	Medical group	PPS	Medical group
		PTAS group		PTAS group	
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				

Items	Indications	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	Outcome Event (%)				
	Loss (%)				
	Mortality				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

472 Note: Cox regression adjusted for variables

473

474 Figure 7 3-year rate of the same-territory stroke (KM curve) (FAS)7

475

476 Figure 8 3-year rate of the same-territory stroke (KM curve) (PPS)8

477 Table 13 Changes of neurological function evaluation (mRS and NIHSS score)¹³

Items	Follow-up time	Indicators	Total	Experimental group	Control group	P
NIHSS	Baseline	Median (IntQ)				
	1 day after randomization	Median (IntQ)				
	7 days after randomization	Median (IntQ)				
	1 month after randomization	Median (IntQ)				
	12 months after randomization	Median (IntQ)				
	24 months after randomization	Median (IntQ)				
	36 months after randomization	Median (IntQ)				
NIHSS	1 day after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	7 days after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	1 month after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				

Items	Follow-up time	Indicators	Total	Experimental group	Control group	P
	12 months after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	24 months after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
	36 months after randomization	Not deteriorate n (%)				
		Deterioration of n (%)				
		P values				
mRS	Baseline	Median (IntQ)				
	7 days after randomization	Median (IntQ)				
	1 month after randomization	Median (IntQ)				
	12 months after randomization	Median (IntQ)				
	24 months after randomization	Median (IntQ)				
	36 months after randomization	Median (IntQ)				
mRS	7 days after randomization	0-2 n (%)				
		3-6 n (%)				

Items	Follow-up time	Indicators	Total	Experimental group	Control group	P
		P values				
	1 month after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				
	12 months after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				
	24 months after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				
	36 months after randomization	0-2 n (%)				
		3-6 n (%)				
		P values				

478

479

480 Table 14 any stroke, severe TIA, cardiovascular events related to stenting or medical therapy within a follow-up of 3 years¹⁴

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Any stroke,	No n (%)				
severe TIA,	Yes n (%)				
cardiovascular	N (Missing)				
events related	Difference of inter-group				
to stenting or	rate 95%CI				
medical therapy	Test Statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

481 Note: Cox regression adjusted for variables

482

483 **8.4 Safety analysis**

484 **8.4.1 Adverse events**

485 Table 15 Summary of adverse events¹⁵

Items	PTAS group			Medical group			P values
	cases	total	percentage	cases	total	percentage	
Adverse events							
Adverse events related to interventions							
Serious Adverse Events							
Serious adverse events associated with interventions							
Adverse events leading to shedding							

486 Note: Adverse reactions associated with experimental drugs are defined as likely, likely, and definitely related.

487

488

489

490 Table 16 Summary of the severity of adverse events16

Items	PTAS group			Medical group			P values
	cases	total	percentage	cases	total	percentage	
Mild Adverse Events							
Moderate Adverse Events							
Major Adverse Events							

491

492

493 **China Angioplasty & Stenting for Symptomatic Intracranial Severe**
494 **Stenosis (CASSISS)**

495
496 **A prospective multi-center, randomized controlled trial (RCT)**

497

498 **Statistical Analysis**

499 **Plan**

499

500

501

Ver. 2.0

502

Version date: December 19, 2020

503

Type of research:	Investigator-initiated Phase IV clinical trial
Organizer:	Xuanwu Hospital Capital Medical University
Statistical analysis:	Clinical Research Institute Peking University

504

505 **Author:** _____

506 **Date:** _____

507 **Haibo Wang**

508 **Clinical Research Institute of Peking University**

509

510

CONTENTS

511	1. ABBREVIATIONS	5
512	2. PROTOCOL ABSTRACT.....	7
513	2.1 STUDY PURPOSE	7
514	2.2 STUDY DESIGN.....	7
515	2.3 SAMPLE SIZE	7
516	2.4 BLINDING AND RANDOMIZATION	8
517	2.5 INTERVENTIONS	8
518	2.6 STUDY POPULATION AND DIAGNOSTIC CRITERIA.....	9
519	2.6.1 Inclusion criteria.....	9
520	2.6.2 Exclusion criteria	10
521	3. ASSESSMENT OF OUTCOME EVALUATION.....	14
522	3.1 OUTCOME EVALUATION.....	14
523	3.1.1 <i>Primary Outcome</i>	14
524	3.1.2 <i>Secondary Outcomes</i>	14
525	3.2 SAFETY OUTCOMES.....	14
526	4. DATA SAFETY MONITORING BOARD (DSMB).....	16
527	5. ANALYSIS DATA SET.....	17
528	6. PROCESSING OF MISSING DATA	18
529	7. STATISTICAL ANALYSIS METHOD.....	19
530	7.1 GENERAL PRINCIPLES OF STATISTICAL ANALYSIS	19
531	7.2 ANALYSIS PLAN	19
532	7.3 COMPLETION	20
533	7.4 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS	20
534	7.5 EFFICACY ANALYSIS.....	20
535	7.5.1 Main Efficacy index.....	20
536	7.5.2 Secodary Efficacy index.....	21
537	7.5.3 <i>Others</i>	21
538	7.6 SAFETY ANALYSIS	22
539	8. STATISTICAL ANALYSIS RESULTS	23
540	8.1 DISTRIBUTION OF INCLUDED PATIENTS	23
541	8.2 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS	26
542	8.3 EFFICACY EVALUATION	32
543	8.3.1 <i>Primary efficacy outcome</i>	32
544	8.3.2 Secondary efficacy outcomes.....	33

545	8.4 SAFETY ANALYSIS	39
546	8.4.1 ADVERSE EVENTS.....	39
547		
548		

549

APPENDIX

550	TABLE 1 POPULATION DISTRIBUTION OF EACH CENTER.....	23
551	TABLE 2 LIST OF PATIENTS NOT INCLUDED IN THE FAS/PPS SET.....	24
552	TABLE 3 DATA SETS OF ENROLLED PATIENTS AND SAFETY AND EFFICACY ANALYSIS SETS.	
553	24
554	TABLE 4 DEMOGRAPHIC DATA	26
555	TABLE 5 BASELINE INFORMATION	26
556	TABLE 6 PAST MEDICAL HISTORY	28
557	TABLE 7 HISTORY OF PREVIOUS AND CURRENT MEDICAL THERAPY FOR	
558	CEREBROVASCULAR DISEASES	29
559	TABLE 8 MEDICAL RECORDS OF THE PRESENT ISCHEMIC ATTACK.....	29
560	TABLE 9 INCIDENCE OF PRIMARY OUTCOME (STROKE OR DEATH) 12 MONTHS AFTER	
561	RANDOMIZATION	32
562	TABLE 10 INCIDENCE OF DISABLING STROKE OR DEATH WITHIN 36 MONTHS AFTER	
563	RANDOMIZATION	33
564	TABLE 11 2-YEAR RATE OF THE SAME-TERRITORY STROKE.....	35
565	TABLE 12 3-YEAR RATE OF THE SAME-TERRITORY STROKE	36
566	TABLE 13 ANY STROKE, SEVERE TIA, CARDIOVASCULAR EVENTS RELATED TO STENTING OR	
567	MEDICAL THERAPY WITHIN A FOLLOW-UP OF 3 YEARS	38
568	TABLE 14 SUMMARY OF ADVERSE EVENTS	39
569	TABLE 15 SUMMARY OF THE SEVERITY OF ADVERSE EVENTS.....	40
570		

572 **1. Abbreviations**

ALT	Serum alanine aminotransferase
AST	Serum glutamic-oxalacetic transaminase
APTT	Activated partial thromboplastin time
BUN	Urea nitrogen (blood)
BMI	Body mass index
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CRF	Case report form
CRO	Contract Research Organization
CT	Computed tomography
CTA	Computed tomography angiography
CTP	CT perfusion scan
DSA	Digital subtraction angiography
DSMB	Data Safety Monitoring Board
DWI	Magnetic resonance diffusion weighted imaging
EC	Ethics committee
ECG	Electrocardiogram
FAS	Full analysis set
FBS	Fasting plasma glucose
HDL-C	High density lipoprotein cholesterol
ICF	Informed consent
INR	International standard ratio
ITT	Intention to treat
LDL-C	Low density lipoprotein cholesterol
LOCF	The last observation was carried forward
MCA	Middle cerebral artery
MedDRA	Dictionary of medical terms used for drug registration

MRA	Nuclear magnetic angiography
mRS	Modified Rankin Scale
MTT	Mean transit time
NIHSS	National Institutes of Health Stroke Assessment Scale
PET	Positron emission tomography
PPS	Per-protocol set
PT	Prothrombin time
PWI	Perfusion-weighted imaging
RCT	Randomized controlled trial
SFDA	State Food and Drug Administration
TCD	Transcranial Doppler scan
TIA	Transient ischemic attack
XeCT	Xenon enhanced computed tomography

573

574

575 **2. Protocol Abstract**

576 **2.1 Study purpose**

577 Main purpose: to determine whether PTAS (using the Gateway PTA balloon catheter
578 and Wingspan Stent System, Stryker, Fremont, CA, USA) combined with medical
579 therapy is superior to medical therapy alone for preventing the primary outcome
580 (stroke or death within 30 days after enrollment, or stroke in the territory of the
581 symptomatic intracranial artery between 30 days through 1 year in patients with
582 recent TIA or non-disabling stroke caused by 70% to 99% stenosis of a major
583 intracranial artery).

584

585 Secondary purpose: to compare outcomes between groups in terms of:

- 586 ☞ Disabling stroke or death after enrollment through 3 years in both arms;
- 587 ☞ 2-year rate of the same-territory stroke;
- 588 ☞ 3-year rate of the same-territory stroke;
- 589 ☞ Any stroke, TIA, or cardiovascular events within a follow-up of 3 years;
- 590 ☞ Death rate in both arms within a follow-up of 3 years.

591

592 **2.2 Study design**

593 This study is a multicenter, randomized, open-label, outcome-blinded trial comparing
594 medical therapy alone or medical therapy plus stenting with the use of the Wingspan
595 Stent system in patients with transient ischemic attack (TIA) or non-disabling
596 ischemic stroke caused by 70%-99% stenosis of a major intracranial artery.

597

598 **2.3 Sample size**

599 For symptomatic severe (70-99%) intracranial atherosclerotic stenosis, 1 year of
600 ipsilateral stroke risk in medical therapy group WASID study was 18%, which was
601 7.3% in a study by the Wingspan stent therapy (Wei-jian Jiang, etc.). At a significance

602 level of 5% on both sides, the absolute difference of 10.7% (relative risk reduction:
603 59%), and a power of 80%, within 12 months of follow-up, a total of 302 patients
604 needs to be evaluated. Assuming a 20% incidence of loss of follow-up and/or
605 withdrawal, a total of 380 patients, 190 per group, are required to be enrolled in this
606 study.

607

608 **2.4 Blinding and randomization**

609 Complete randomization methodology will be used. Once the patient meets the
610 inclusion criteria after signing the informed consent form, the researcher will
611 immediately make a phone call to the research group, and the answering staff will
612 assign the patient a random number according to the patient number, and the random
613 number will associate the patient with the corresponding treatment group. Patients
614 will be given medical therapy alone or Wingspan stent plus medical therapy,
615 depending on the treatment group randomly assigned. Patients randomly assigned to
616 the medical treatment group will be discharged after DSA examination.

617 This study is an open, outcome-blinded study.

618

619 **2.5 Interventions**

620 Medical therapy:

621 Medical therapy will be identical in both arms and will be similar to the previously
622 described risk factor management for the SAMMPRIS trial. In brief, aspirin 100 mg
623 plus clopidogrel 75 mg per day for 90 days (aspirin 100 mg or clopidogrel 75 mg
624 alone per day thereafter) and management of risk factors. Medical management of
625 risk factors consists of control of low-density lipoprotein (LDL-C) (target:
626 LDL-C<2.58mmol/L (100 mg/dL) with statins, and hypertension (systolic pressure
627 <140 mmHg [<130 mmHg in the case of patients with diabetes] and diastolic pressure
628 <90 mmHg) based on 2014 AHA/ASA guidelines.

629

630 Stenting:

631 Patients randomized to stenting will be scheduled for intervention within three to five
632 business days. The study protocol requires that the stenting procedure be performed
633 under general anesthesia by a qualified operator at each site. Intensive management
634 of risk factors will be applied thereafter.

635

636 **2.6 Study population and diagnostic criteria**

637 This trial aims to recruit patients who have had a TIA or ischemic stroke ($mRS \leq 2$) and
638 advanced ICAS (70%–99% on angiogram). Catheter angiography is required to
639 confirm 70%–99% stenosis by the WASID criterion for a patient to qualify. Patients
640 who have an ischemic stroke within the last three weeks will not be included because
641 of concern for hemorrhagic transformation.

642

643 **2.6.1 Inclusion criteria**

644 Detailed inclusion criteria were as follows:

645 14. Eligible patients aged between 30 and 80 years; intracranial arterial stenosis
646 related to the following non-atherosclerotic factors will be not be considered:
647 arterial dissection, moya-moya disease; vasculitic disease; herpes zoster,
648 varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial
649 infection; any intracranial stenosis associated with cerebrospinal fluid pleocytosis;
650 radiation-induced vasculopathy; fibromuscular dysplasia; sickle cell disease;
651 neurofibromatosis; benign angiopathy of central nervous system; postpartum
652 angiopathy; suspected vasospastic process, and suspected recanalized
653 embolus;

654 15. Symptomatic intracranial stenosis: presented with transient ischemic stroke (TIA)
655 or stroke within the past 12 months attributed to 70%-99% stenosis of a major
656 intracranial artery (ICA, MCA [M1], vertebral artery, or basilar artery [BA]);

- 657 16. Degree of stenosis: 70%–99%; stenosis degree must be confirmed by catheter
658 angiography for enrollment in the trial;
- 659 17. Remote infarctions on MRI scan, which can be accounted for by the occlusion of
660 the terminal cortical branches or hemodynamic compromise (perforator occlusion
661 excluded). Infarction due to perforators occlusion is defined as basal ganglia or
662 brainstem/thalamus infarction related with M1 or BA stenosis;
- 663 18. Expected ability to deliver the stent to the lesion;
- 664 19. All the patients should be performed with stenting beyond a duration of three
665 weeks from the latest ischemic symptom onset;
- 666 20. No recent infarctions identified on MRI (indicated as high signals on DWI series)
667 upon enrollment;
- 668 21. No massive cerebral infarction (>1/2 MCA territory), intracranial hemorrhage,
669 epidural or sub-dural hemorrhage, and intracranial brain tumor on CT or MRI
670 scan;
- 671 22. mRS scale score of ≤ 2 ;
- 672 23. Target vessel reference diameter must be measured to be 2.00 mm to 4.50 mm;
673 target area of stenosis is ≤ 14 mm in length;
- 674 24. No childbearing potential or has a negative pregnancy test within the past one
675 week prior to study procedure; female patients had normal menses in the last 18
676 months;
- 677 25. Patient is willing and able to return for all follow-up visits required by the protocol;
- 678 26. Patients understand the purpose and requirements of the study and have signed
679 informed consent form.

680

681 **2.6.2 Exclusion criteria**

682 Detailed exclusion criteria were as follows:

-
- 683 30. Refractory to general anesthesia; not able to be overcome by pre-treatment with
684 medical therapy
- 685 31. Any condition that precludes proper angiographic assessment
- 686 32. Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is
687 proximal or distal to the target intracranial lesion
- 688 33. Bilateral intracranial VA stenosis of 70%–99% and uncertainty about which lesion
689 is symptomatic (for example, if patient has pon, midbrain, temporal and occipital
690 symptoms)
- 691 34. Presence of a previously placed intravascular stent or graft in the ipsilateral
692 distribution within 30 days
- 693 35. Previous treatment of target lesion with a stent, angioplasty, or other mechanical
694 device, or plan to perform staged angioplasty followed by stenting of target lesion
- 695 36. Severe vascular tortuosity or anatomy that would preclude the safe introduction of
696 a guiding catheter, guiding sheath or stent placement
- 697 37. Plan to perform concomitant angioplasty or stenting of an extracranial vessel
698 tandem to an ipsilateral intracranial stenosis
- 699 38. Presence of intraluminal thrombus proximal to or at the target lesion
- 700 39. Any aneurysm proximal to or distal to intracranial stenotic artery
- 701 40. Intracranial tumors or any intracranial vascular malformations
- 702 41. Computed tomographic or angiographic evidence of severe calcification at target
703 lesion
- 704 42. Thrombolytic therapy within 24 hours before enrollment
- 705 43. Evolving stroke or progressive neurologic signs within 24 hours before enrollment
- 706 44. Stroke of sufficient size (>5 cm on CT or MRI) to place patient at risk of
707 hemorrhagic transformation during the procedure; hemorrhagic transformation of
708 an ischemic stroke within the past 15 days

- 709 45. Previous spontaneous intracerebral (parenchymal) or other intracranial
710 (subarachnoid, subdural, or epidural) hemorrhage within 30 days
- 711 46. Untreated chronic subdural hematoma >5 mm in thickness
- 712 47. Other cardiac sources of emboli such as left ventricular aneurysms, intracardiac
713 filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcified
714 aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal
715 aneurysm, left atrial myxoma
- 716 48. Myocardial infarction within previous 30 days
- 717 49. Chronic atrial fibrillation; any episode of paroxysmal atrial fibrillation within the
718 past six months, or history of paroxysmal atrial fibrillation requiring chronic
719 anticoagulation
- 720 50. Intolerance or allergic reaction to any of the medical therapy, including aspirin,
721 clopidogrel, heparin, and local or general anesthetics
- 722 51. History of life-threatening allergy to contrast medium. If not life threatening and
723 can be effectively pre-treated, patient can be enrolled at physicians' discretion
- 724 52. Recent gastrointestinal bleed that would interfere with antiplatelet therapy
- 725 53. Active bleeding diathesis or coagulopathy; active peptic ulcer disease, major
726 systemic hemorrhage within 30 days, active bleeding diathesis, platelets count
727 <125,000, hematocrit <30, Hgb <10 g/dl, uncorrected INR >1.5, bleeding time >1
728 minute beyond upper limit normal, or heparin-associated thrombocytopenia that
729 increases the risk of bleeding, uncontrolled severe hypertension (systolic
730 BP>180mm hg or diastolic BP>115mm hg), severe liver impairment (AST or 25.
731 ALT >3 times normal, cirrhosis), creatinine >265.2 mmol/l (unless on dialysis).
732 Major surgery (including open femoral, aortic, or carotid surgery) within previous
733 30 days or planned in the next 90 days after enrollment
- 734 54. Indication for warfarin or heparin beyond enrollment (exceptions allowed for use
735 of systemic heparin during stenting procedure or subcutaneous heparin for deep
736 venous thrombosis prophylaxis while hospitalized)

737 55. Inability to understand and cooperate with study procedures or sign informed
738 consent

739 56. Severe dementia or psychiatric problems that prevent the patients from following
740 an outpatient program reliably

741 57. Pregnancy or of childbearing potential and unwilling to use contraception for the
742 duration of this study

743 58. Actively participating in another drug or device trial that has not completed the
744 required protocol follow-up period

745

746 **3. Assessment of Outcome evaluation**

747 **3.1 Outcome evaluation**

748 3.1.1 Primary Outcome

749 Stroke or death within 30 days after enrollment or stroke in the territory of qualifying
750 artery (SIT) beyond 30 days through 1 year.

751

752 3.1.2 Secondary Outcomes

753 ☞ Disabling stroke or death within 3 years after randomization;

754 ☞ 2-year rate of SIT;

755 ☞ 3-year rate of SIT;

756 ☞ Death rate within 3 years;

757 ☞ Any stroke, TIA, or cardiovascular events within 3 years.

758

759 **Note**

760 Stroke is defined as the rapid loss of brain function due to disturbance in the blood
761 supply to the brain that persists beyond 24 hours. This can be due to ischemia or
762 hemorrhage.

763

764 TIA is defined as rapidly developed clinical signs of focal or global disturbance of
765 cerebral function lasting longer than 10 minutes but fewer than 24 hours, with no
766 apparent nonvascular cause.

767

768 **3.2 Safety outcomes**

769 Investigators should take appropriate treatment for AEs to ensure the safety of
770 patients and track all AEs/SAEs until they are properly resolved, or the condition is
771 stable. Additional medical procedures and/or referral to a medical specialist may be

772 required to confirm whether the patients are qualified to continue to participate in the
773 study.

774

775 **4. Data Safety Monitoring Board (DSMB)**

776 An independent data safety monitoring committee composed of experts in
777 neurosurgery, internal medicine, neuroradiology, and biostatistics who are not
778 involved in the study is responsible for the following:

779 1. All potential outcome events including TIA, stroke, and death will be reviewed and
780 confirmed. Clinical records and imaging results related to any outcomes are required
781 to be emailed to the outcome committee, and the outcome committee's decision will
782 be the final decision.

783 2. Efficacy and safety data, as well as balance of patient benefits and risks will be
784 reviewed regularly. Timely recommendations will be given to the executive committee
785 on whether to continue, modify, or discontinue the study.

786

787 **5. Analysis data set**

788 Full Analysis Set (FAS): all the subjects who are randomized into groups will be
789 included, except the subjects who do not meet the inclusion and exclusion criteria and
790 who are withdrawn immediately after randomization without receiving any intervention
791 will be excluded. According to the intention-to-treat (ITT) principle, all randomized
792 patients will be analyzed according to the treatment group assigned to them at the
793 time of randomization.

794

795 Per-protocol Set (PPS): All patients who are treated according to the study protocol
796 (the eligibility criteria, the assigned treatment after randomization, additional
797 medication protocol, the follow-up protocol, and completion of the case report form).

798

799 Safety Analysis Set (SAS): Randomized patients who receive at least one dose of
800 antiplatelet therapy with a documented safety outcome.

801

802 Efficacy analysis will be carried out based on the FAS and the PPS, and the
803 conclusions will be made based on the FAS. All baseline demographic data analyses
804 will be performed on the basis of the FAS and safety assessments will be performed
805 on the SAS.

806

807 **6. Processing of missing data**

808 For patients who die or are lost to follow-up within 36 months after randomization, the
809 30-day, 12-month, and 36-month NIHSS and mRS score will be filled using the last
810 observed value (LOCF) method. For other missing data, no filling or other processing
811 will be conducted. For survival analysis, missing data will be considered as censored.
812

813 **7. Statistical analysis method**

814 **7.1 General principles of statistical analysis**

815 Prior to database locking, the statistician is responsible for developing a statistical
816 analysis plan in consultation with the principal investigator. SAS 9.4 statistical
817 software will be used. The efficacy evaluation includes the analysis of PPS and FAS
818 sets, and the conclusion will be based on the FAS set. SAS set analysis will be used
819 for safety evaluation.

820

821 All statistical tests will be conducted using a two-sided test, and a p-value of 0.05 or
822 less will be considered statistically significant (unless otherwise specified).

823 For patients who cross groups, that is, the actual group is not consistent with the
824 randomly assigned group, efficacy will be analyzed according to the ITT principle
825 based on the FAS, and safety will be analyzed according to the SAS.

826

827 **7.2 Analysis plan**

828 After the study protocol is finalized, the statistician will develop the statistical analysis
829 plan in consultation with the principal investigator. All the analyses will be performed
830 with the use of SAS software, version 9.4 (SAS Institute, license number: 11202165).

831

832 Numerical variables will be presented with mean, standard deviation (normally
833 distributed), or median (interquartile interval). Categorical and hierarchical variables
834 will be presented with the number of cases and percentages.

835

836 Appropriate method for comparison of baseline between two groups will be adopted
837 according to the types of variables, and the comparison of numerical variables will be
838 tested with t-test (normal distribution) or Wilcoxon rank test according to the data
839 distribution, categorical variables with chi-square test or the exact probability method

840 (if a chi-square test is not applicable), hierarchical data with Wilcoxon rank test or
841 CMH.

842 **7.3 Completion**

843 The number of patients enrolled in each center, the number of patients who complete
844 the trial and the number of patients withdrawn from the trial will be summarized, and
845 the list of patients not included in the FAS/PPS set and the reasons for exclusion will
846 be listed. The number of cases in each group FAS/PPS dataset, the distribution of
847 cases in each center, and a detailed list of incomplete causes will be listed.

848

849 **7.4 Demographic data and baseline characteristics**

850 Baseline data such as patient demographic characteristics (age and gender), vital
851 signs, past medical history, treatment history and current medical history will be
852 described, and baseline data such as age, gender and BMI of the two groups will be
853 compared to measure the comparability of the two groups.

854

855 **7.5 Efficacy analysis**

856 FAS and PPS will be used for efficacy analysis.

857 **7.5.1 Main Efficacy index**

858 Stroke or death within 30 days after randomization; And stroke in the territory of
859 qualifying artery (SIT) beyond 30 days through 12 months after randomization.

860

861 The incidence of stroke or death at 12 months will be compared between the medical
862 therapy group and the stent group, and a 95% confidence interval will be calculated
863 for the difference between the two groups. CMH Chi-square test considering
864 multicenter design will be adopted for inter-group comparison. If the impact of other

865 factors is adjusted, Logistics regression model can be considered for inter-group
866 comparison.

867

868 The Log Rank test will be used to analyze the primary efficacy outcomes, and the
869 center information will be stratified as covariates. The Cox proportional risk model will
870 be used to calculate HR and its 95% confidence interval (CI) to estimate efficacy. The
871 model included the same covariates as the Log Rank test for fitting. Kaplan-Meier
872 curves will be plotted by treatment group.

873

874 For comparison of patient demographic characteristics (age, gender), vital signs,
875 medical history, history of treatment and the medical records of baseline data
876 between groups, if there are important significant differences for baseline data, the
877 Cox proportional hazards model will be used for adjustment of these baseline
878 variables, which will be included as a sensitivity analysis.

879

880 **7.5.2 Secodary Efficacy index**

881 Disabling stroke or death after enrollment within 3 years in both arms; 2) 2-year rate
882 of SIT; 3) 3-year rate of SIT; 4) any stroke, TIA, or cardiovascular events within 3
883 years; 5) survival rate within 3 years. All above will be analyzed using the same
884 method as the primary efficacy outcomes. The incidence of each outcome and the
885 95% confidence interval will be described by groups.

886

887 **7.5.3 Others**

888 At the same time, the dichotomous variables will be transformed by selecting clinically
889 significant cut-off points for inter-group comparison. CMH Chi-square test considering
890 multicenter design will be adopted for inter-group comparison. If other factors are
891 adjusted, Logistics regression model can be considered for inter-group comparison.

892

893 **7.6 Safety analysis**

894 The safety evaluation will be analyzed on the SAS dataset.

895 The number of adverse events of the two groups, as well as the incidence of adverse
896 events, serious adverse events will be described in tables. The changes of laboratory
897 and ECG will be described in tables. Procedure-related complications within 30 days
898 after operation in the stent group will be analyzed. Chi-square test/Fisher exact test
899 will be used to compare the incidence of adverse events and the incidence of serious
900 adverse events between the two groups.

901

902 **8. Statistical analysis results**

903 **8.1 Distribution of included patients**

904 Table 1 Population distribution of each center17

	FAS			PPS			SS (Actual Group)		
Center	PTAS group	Medical group	Total	PTAS group	Medical group	Total	PTAS group	Medical group	Total
Total number									

905

906

907

908 Table 2 List of patients not included in the FAS/PPS set18

				Included in analysis dataset		
Center	Patient ID	Time of enrollment	Reason of exclusion	PPS	FAS	SS

909

910 Table 3 Data sets of enrolled patients and safety and efficacy analysis sets.19

	Items	PTAS group	Medical group	Total
The whole data set				
	Randomly enrollment			
Not included in the FAS set				
	Failure to meet inclusion/exclusion criteria			
	Exit after randomization			
Suspension during study				
	Upon requests from subjects or subject's legal authorized representatives.			
	lost of follow-up			
	Crossover			
	Failure to follow the plan			
	Other			
Safety analysis set				
	SS (Actual Group)			
Efficacy analysis set				

	FAS			
	PPS			

911

912

913 **8.2 Demographic data and baseline characteristics**

914 Table 4 Demographic data²⁰

Items	Indicators	Total	PTAS group	Medical group	P
Age (years)	Mean (SD)				
Gender	Male, n (%)				
	Female, n (%)				
Ethnicity	Han, n (%)				
	Other, n (%)				

915

916

917 Table 5 Baseline information²¹

Items	Indicators	Total	PTAS group	Medical group	P
Systolic blood pressure (mmHg)	Mean (SD)				
Diastolic blood pressure (mmHg)	Mean (SD)				
Heart rate (times per minute)	Mean (SD)				
BMI (kg/m ²)	Mean (SD)				
Smoking history	None n (%)				

Items	Indicators	Total	PTAS group	Medical group	P
	Previous n (%)				
	Current n (%)				
Alcohol use	No n (%)				
	Previous n (%)				
	Current n (%)				
Family history of cerebrovascular disease	No n (%)				
	Yes n (%)				
Family history of cardiovascular disease	No n (%)				
	Yes n (%)				
High density lipoprotein cholesterol	Mean (SD)				
Low density lipoprotein cholesterol	Mean (SD)				
Total cholesterol	Mean (SD)				
triglycerides	Mean (SD)				
C-reactive protein	Mean (SD)				
HbA1c	Mean (SD)				

919

 920 Table 6 Past medical history²²

Items	Indicators	Total	PTAS group	Medical group	P
Hypertension	No n (%)				
	Yes n (%)				
Diabetes	No n (%)				
	Yes n (%)				
Hyperlipidemia	No n (%)				
	Yes n (%)				
Coronary heart disease (CHD)	No n (%)				
	Yes n (%)				
Myocardial infarction	No n (%)				
	Yes n (%)				
Atrial fibrillation	No n (%)				
	Yes n (%)				
Peripheral vascular disease	No n (%)				
	Yes n (%)				
Alimentary ulcer	No n (%)				
	Yes n (%)				

921

922

 923 Table 7 History of previous and current medical therapy for cerebrovascular diseases²³

Items	Indicators	Total	PTAS group	Medical group	P
Antiplatelet agent	No n (%)				
	Yes n (%)				
Anticoagulant drugs	No n (%)				
	Yes n (%)				
History of radiotherapy for cerebrovascular disease	No n (%)				
	Yes n (%)				
History of surgical treatment of cerebrovascular disease	No n (%)				
	Yes n (%)				

924

925

 926 Table 8 Medical records of the present ischemic attack.²⁴

Items	Indicators	Total	PTAS group	Medical group	P
-------	------------	-------	------------	---------------	---

Items	Indicators	Total	PTAS group	Medical group	P
Ischemia-cerebrovascular disease occurred within 12 months	Cerebral infarction n (%)				
	TIA n (%)				
Time from symptom onset to randomization	Median (IntQ)				
Artery stenosis	Intracranial segment of internal carotid artery N (%)				
	Middle cerebral artery N (%)				
	Intracranial segment of vertebral artery N (%)				
	Basilar artery N (%)				
	Others n (%)				
Stenosis degree	Median (IntQ)				
	70-79% n (%)				
	80-89% n (%)				
	90-99% n (%)				
Mori classification	Short of n (%)				

Items	Indications	Total	PTAS group	Medical group	P
	Tubular n (%)				
	Dispersion of n (%)				
mRS score	Median (IntQ)				
NIHSS score	Median (IntQ)				

927

928

929 **8.3 Efficacy evaluation**

930 8.3.1 Primary efficacy outcome

931 Table 9 Incidence of primary outcome (stroke or death) 12 months after randomization²⁵

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Stroke or death	or No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95% CI				
	Testing statistic (CMH)				
	P value				
	Outcome Event (%)				
	Loss (%)				
	Incidence				
	95%CI				
	Log - rank test				
	P values				

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Cox regression	Hazard Ratio				
	95% CI				
	P values				
Cox regression (sensitivity analysis)	Hazard Ratio				
	95%CI				
	P values				

932 Note: Cox regression adjusted for variables

933

934 Figure 1 Incidence of primary outcome (stroke or death) within 12 months after randomization (KM curve) (FAS)9

935

936 Figure 2 Incidence of primary end point (stroke or death) within 12 months after randomization (KM curve) (PPS)10

937

938

939 **8.3.2 Secondary efficacy outcomes**

940 Table 10 Incidence of disabling stroke or death within 36 months after randomization26

Items	Indications	FAS		PPS		
		PTAS group	Medical group	PTAS group	Medical group	
Disabling stroke death	No n (%)					
	or Yes n (%)					
	N (Missing)					
	Difference of inter-group rate 95%CI					
	Test statistics (CMH)					
	P values					
	Outcome Event (%)					
	Loss (%)					
	Median event time					
	95% CI					
	Log - rank test					
	P values					
	Cox regression	Hazard Ratio				
		95%CI				
	P values					

941 Note: Cox regression adjusted for variables

942

943 Figure 3 Disabling stroke or death within 36 months after randomization (KM curve) (FAS)11

944

945 Figure 4 Disabling stroke or death within 36 months after randomization (KM curve) (PPS)12

946

947

948

949 Table 11 2-year rate of the same-territory stroke27

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				

Items	Indications	FAS	Medical group	PPS	Medical group
		PTAS group		PTAS group	
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

950 Note: Cox regression adjusted for variables

951

952 Figure 5 2-year rate of the same-territory stroke (KM curve) (FAS)13

953

954 Figure 6 2-year rate of the same-territory stroke (KM curve) (PPS)14

955

956

957 Table 12 3-year rate of the same-territory stroke 28

Items	Indications	FAS	Medical group	PPS	Medical group
		PTAS group		PTAS group	
Same-territory stroke	No n (%)				
	Yes n (%)				
	N (Missing)				

Items	Indications	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
	Difference of inter-group rate 95%CI				
	Test statistics (CMH)				
	P values				
	Outcome Event (%)				
	Loss (%)				
	Mortality				
	95% CI				
	Log - rank test				
	P values				
Cox regression	Hazard Ratio				
	95%CI				
	P values				

958 Note: Cox regression adjusted for variables

959

960 Figure 7 3-year rate of the same-territory stroke (KM curve) (FAS)15

961

962 Figure 8 3-year rate of the same-territory stroke (KM curve) (PPS)16

963
 964 Table 13 any stroke, severe TIA, cardiovascular events related to stenting or medical therapy within a follow-up of 3 years²⁹

Items	Indicators	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
Any stroke, severe TIA, cardiovascular events related to stenting or medical therapy	No n (%)				
	Yes n (%)				
	cardiovascular N (Missing)				
	Difference of inter-group				
	rate 95%CI				
	Test Statistics (CMH)				
	P values				
	No n (%)				
	Outcome Event (%)				
	Loss (%)				
	Median event time				
	95% CI				
	Log - rank test				
P values					
Cox regression	Hazard Ratio				
	95%CI				

Items	Indications	FAS		PPS	
		PTAS group	Medical group	PTAS group	Medical group
P values					

965 Note: Cox regression adjusted for variables

966

967 8.4 Safety analysis

968 8.4.1 Adverse events

969 Table 14 Summary of adverse events³⁰

Items	PTAS group			Medical group			P values
	cases	total	percentage	cases	total	percentage	
Adverse events							
Adverse events related to interventions							
Serious Adverse Events							
Serious adverse events associated with interventions							
Adverse events leading to shedding							

970 Note: Adverse reactions associated with experimental drugs are defined as likely, likely, and definitely related.

971

972 Table 15 Summary of the severity of adverse events³¹

Items	PTAS group			Medical group			P values
	cases	total	percentage	cases	total	percentage	
Mild Adverse Events							
Moderate Adverse Events							
Major Adverse Events							

973

974

975

976

CASSISS Study

977

Statistical Analysis Plan (SAP):

978

Summary of Changes (Ver.1.0 ⇒ Ver.2.0)

979

CASSISS Study: China Angioplasty & Stenting for Symptomatic Intracranial Severe Stenosis

980

Prepared: Dec 19, 2020

#	Page	Item	Description of change(s)		Reasons for change
			Before change (Ver. 1.0 Date prepared: May 10, 2015)	After change (Ver. 2.0 Date prepared: Dec 19, 2020)	
1	14	3.1.2 Secondary Endpoints	<ul style="list-style-type: none"> • Disabling stroke or death within 3 years after randomization; • 2-year rate of SIT; • 3-year rate of SIT; • Any stroke, TIA, or cardiovascular events related to therapy within 3 years; • Death rate within 3 years; • mRS, NIHSS scores of patients. 	<ul style="list-style-type: none"> • Disabling stroke or death within 3 years after randomization; • 2-year rate of SIT; • 3-year rate of SIT; • Any stroke, TIA, or cardiovascular events related to therapy within 3 years; • Death rate within 3 years; 	Due to protocol revisions
2	20-22	7.5	(3) <u>Mixed effects model will be used to</u>	At the same time, the dichotomous variables	Due to

		<p>Efficacy analysis</p> <p><u>compare the changes of neurological function indexes between groups.</u> At the same time, the dichotomous variables will be transformed by selecting clinically significant cut-off points for inter-group comparison. <u>For mRS, 0-2 versus 3-6 will be used. For NIHSS, an increase of 4 points or more from baseline to 12 months will be considered to have deteriorated neurological function.</u></p> <p>CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If other factors are adjusted, Logistics regression model can be considered for inter-group comparison.</p>	<p>will be transformed by selecting clinically significant cut-off points for inter-group comparison. CMH Chi-square test considering multicenter design will be adopted for inter-group comparison. If other factors are adjusted, Logistics regression model can be considered for inter-group comparison.</p>	<p>revision No.1</p>
--	--	--	--	----------------------

3	38	Table 13	Table 13 Changes of neurological function evaluation (mRS and NIHSS score)	Omit this table	Due to revision No.1
---	----	----------	--	-----------------	----------------------

981

982