CSR SYNOPSIS

Sponsor	Astellas Pharma China, Inc.
Name of the Product	Perdipine (Nicardipine Hydrochloride Injection)

Version Date	2014/07/17

Protocol Number: ACN-PD-2012001

Study Title: Randomized Multicenter Phase IV study to compare efficacy and safety of the two dosage regimens of nicardipine hydrochloride injection in hypertensive emergency patients

Principle Investigator: [redacted], Beijing, China

Study Sites: [redacted]

Study Duration: First Patient First Visit: 2013-03-10; Last Patient Last Visit: 2014-01-07.

Study Phase: IV

Objective: To compare the efficacy and safety between nicardipine hydrochloride injection weight-dependence dosage regimen and non weight-dependence dosage regimen in Chinese hypertensive emergency patients.

Method: This non-inferiority study is a prospective multicenter open-label randomized control study. The subjects are hypertensive emergency patients whose blood pressure > 180/120mmHg (SBP/DBP) and complicated with end target organ damage. The key inclusion criterias were: ≥18 years old; SBP≧ 180mmHg and/or DBP≧120mmHg, and evidence or appearance for end organ damage; able and willing to complete the study per protocol, and sign the informed consent form. The key exclusion criterias were: allergic to nicardipine; severe aortic valve stenosis; perioperative hypertension; cerebral vessel deformity, hemangioma, cerebral infarction induced ICH, ICH into ventricle, cerebral trauma complicated with ICH; other conditions may affect patient safety or study result evaluation that determined by the investigator.

Planned patients number is 160. The objective of the study is to compare the efficacy and safety between nicardipine hydrochloride injection weight-dependence dosage regimen and non weight-dependence dosage regimen in Chinese hypertensive emergency patients.

Control Group: The weight-dependence dosage regimen is strictly follow the package insert which approved by SFDA. This regimen is applied to the control group, 0.5-6μg/kg/min, adjust the drop rate according to blood pressure.

Study Group: The non weight-dependence dosage regimen is applied to study group, with 5mg/h initiation, and 2.5mg/h increasing for each time if the target blood pressure not reached.

The primary efficacy endpoint was: the rate of reaching the target blood pressure within 60 minutes administration. Target blood pressure should be set for every patient before randomization according to clinical guideline. The secondary efficacy endpoints were: (1) the rate of reaching target blood pressure within 6 hours administration (per guidelines or consensus recommendation, <=160/100mmHg, ±5mmHg); (2) the number and time of dosage adjustment to reach the target blood pressure.

The study includes 3 stages: screening/baseline, treatment, and follow up. In screening/baseline stage, the eligible patients who fulfiled the inclusion/exclusion criteria and signed the informed consent form were randomized as 1:1 into control group and study group; they were evaluated from vital sign, physical examination, liver and renal function, imageology and ECG. Treatment stage included dosage adjustment phase and maintenance phase;

in dosage adjustment phase, nicardipine hydrochloride was administrated and adjusted the dosage according to different dosage regimen in different groups, until the target blood pressure is reached,. The heart rate and blood pressure was recorded every 5-15 minutes, either after 60 minutes administration of Nicardipine or target blood pressure is reached. The blood pressure and heart rate was monitored every 15 minutes until 2 hours after the administration of Nicardipine.

the maintenance phase was between 2-6 hours after administration, the blood pressure was maintained at 160/100-110mmHg, maintenance dosage was determined by the investigator according to patient's condition, blood pressure and heart rate was recorded.

In follow up phase (after 6 hours?), patients were evaluated from vital sign, physical examination, liver and renal function.

Efficacy data was collected until 6 hours after treatment; safety data was collected until 48 hours after treatment, or patient transferred out from ICU (whichever happen first), any adverse event or abnormal exam result was collected. Concomitant medication and adverse events collected throughout the whole study period.

Inclusion/Exclusion Criteria:

Inclusion Criteria

1. ≥18 years old
2. SBP≧180mmHg and/or DBP≧120mmHg, and evidence or appearance for end organ damage
   Definition of end organ damage includes: chest pain, short breath, upper abdominal discomfort, syncope, dizziness, unclear vision, confusion, hematuria, and ischemia change in ECG
3. Patient is able and willing to complete the study per protocol, and sign the informed consent form

Exclusion Criteria

1. Allergic to nicardipine injection or its ingredient
2. Severe aortic valve stenosis
3. Perioperative hypertension
4. Cerebral vessel deformity, hemangioma, cerebral infarction induced ICH, ICH into ventricle, cerebral trauma complicated with ICH
5. Other conditions may affect patient safety or study result evaluation that determined by the investigator

Study Withdraw Criteria

Patients fulfil the following criteria should be rejected from the study:

1. Blood pressure decreases ＜20/10mmHg within 20 minutes administration of the investigational medication will be judged as treatment failure. Other anti-hypertensive treatment will be applied by investigator’s consideration
2. Obvious hypotension appears during the treatment

3. New diagnose or new finding that make the patient not proper to continue the investigational medication, judged by the investigator
4. Patient withdraws the informed consent.

Investigational Medication, Dosage and Administration Regimen:

Nicardipine 10mg in 10mL ampoule, intravenous injection. In control group, the dosage adjustment strictly follow the package insert which was approved by SFDA, 0.5-6μg/kg/min, adjust drop rate according to the blood pressure. In study group, dosage adjustment of nicardipine is not depended on patient's body weight, with a 5mg/h initial dosage, increase 2.5mg/h each time if the target blood pressure is not reached.

Comparative Medication, Dosage and Administration Regimen: Not applicable.

Treatment Duration: 6 hours.

Evaluation Endpoints:

Efficacy Evaluation

In this study, blood pressure and heart rate is examined every 5-15 minutes until administration for 60 minutes or reach the target blood pressure. Thereafter, they are examined every 15 minutes until administration for 2 hours.

Primary efficacy endpoint: the rate of reaching the target blood pressure within 60 minutes administration. Target blood pressure should be set for every patient before randomization according to clinical guideline.

Secondary efficacy endpoints:

1) The rate of reaching target blood pressure within 6 hours administration (per guidelines or consensus recommendation, <=160/100mmHg, ±5mmHg)

2) The number and time of dosage adjustment to reach the target blood pressure

Safety Evaluation

Safety evaluation includes adverse event, vital sign, physical examination (height, weight), lab test (liver and renal function), and ECG (if needed).

Statistic Method:

Sample Size: According to the previous study data, for non weight-dependence dosage adjustment, 92% reach the target blood pressure within 1 hour, which is 90% for weight-dependence dosage adjustment. This study is non-inferior design, expecting 80% power to show study group is non-inferior than the control group. Assume α=0.05, and equivalence margin is 0.1, according to 1:1 ratio, 71 patients are needed for each group. Considering less than 5% patient not eligible or drop off, 80 patients are planned to be enrolled for each group, which make 160 in total.

Number of Patients:

Patients planned: 160 (80 for each group)

Patients enrolled: 163

1 patient in control group (CRF No. [redacted]) is the same patient of No. [redacted], i.e. repeat enroll; 2 patients in study group (CRF No. [redacted] and [redacted]) did not take investigational medication, didn't enter FAS and SS. Thus, there were 80 patients in control group and study group respectively entered safety set (SS) and full analysis set (FAS). There were 5 (6.17%) and 6 (7.32%) did not enter per-protocol set (PPS) in control group and study group respectively. Refer to the table below for detail.

Analysis data set

	Control group	Study group
Plan	80	80
Enroll	81(100)	82(100)
Safety set (SS)	80(98.77)	80(97.56)
Full analysis set (FAS)	80(98.77)	80(97.56)
Per-protocol set (PPS)	76(93.83)	76(92.68)

Analysis Sets:

Full Analysis Set (FAS)

The FAS included patients who received randomized assignment, at least 1 dose of study medication, and at least 1 efficacy assessment. The FAS was used as the major set for efficacy analysis of this study.

Per Protocol Set (PPS)

The PPS was a sub-set of the FAS and included patients in FAS who didn't have significant protocol

deviation, who had good compliance, and who did not miss the primary efficacy endpoint. Patients discontinued due to lack of efficacy were included in PPS. The PPS was used as the secondary set for efficacy analysis of this study.

Safety Set (SS)

The SS included patients who received randomized assignment, at least 1 dose of study medication, and at least 1 safety assessment. The SS was used as the major set for safety analysis of this study.

Result:

Study Population:

This study enrolled 163 patients in 9 sites in China. 152 (93.25%) patients completed the study. 11 (6.75%) patients early discontinued, 4 in control group and 7 in study group. Reason for the early discontinuation included: protocol deviation or not eligible for in/exclusion criteria - 1 (0.61%), other adverse events - 1 (0.61%), treatment failure - 2 (1.23%), withdraw informed consent – 1 (0.61%), other reasons – 6 (3.68%).

Among 160 patients in FAS set, the ratio between male and female was 43.75% vs 56.25% in control group, and 46.25% vs 53.75% in study group, the average age was 59.96±16.16 in control group, and 62.90±15.92 in study group, the average height was 164.35±8.51cm in control group, and 165.32±8.50cm in study group, the average weight was 66.86±14.67kg in control group, and 69.86±17.00kg in study group. At the time of enrollment, the average SBP was 198.99±14.57mmHg and 198.50±15.76mmHg in control and study group respectively, the average DBP was 110.44±19.01mmHg and 106.93±20.28 mmHg in control and study group respectively. The main complains included vertigo, headache, nausea and vomit, dizziness, chest pain, chest stuffiness, unclear vision, pallor or flushing. The average time interval between symptom onset and attendance visit to the doctor? was 1928.5±5415.9min in control group, and 1556.6±3803.3min in study group. Regularly taken anti-hypertensive medications mainly included CCB, ACEI, ARB, β-BLOCKER and diuretics.

In FAS, The average interval between symptom on set and medication initiation was 2115.8±5165.7min in control group, and 1082.4±2242.6min in study group. The duration from medication initiation to end of treatment was 397.48±285.34min in control group, and 412.26±356.50min in study

group.

Efficacy Results:

In FAS, in the control group 85% reached the target blood pressure within 1 hour as compared to 92.5% in study group. Tested by non-inferior comparing the rate between the 2 groups, $P<0.025$, suggesting the dosage adjustment method of study group not inferior than the control group. Tested by confidence interval estimation, the study group statistically non-inferior to the control group. The results were consistent in 2 test methods, which suggested the non weight-dependence dosage regimen was non-inferior to the weight-dependence regimen in nicardipine treatment of hypertensive emergency of Chinese. Data in PPS was similar to the data in FAS.

In FAS, the rate of reaching target blood pressure within 6 hours was 100% in both groups, which suggested the non weight-dependence dosage regimen had the same efficacy as to the weight-dependence regimen.

The average number of dosage adjustments to reach target blood pressure was 0.82±1.00 in control group, and 0.71±0.83 in study group, without statistical significance ($P=0.4493$). The average time of dosage adjustments to reach target blood pressure was 43.42±55.94min in control group, and 26.39±30.82min in study group, t test between groups, $P=0.02$, which suggested statistical significance, that the non weight-denpendence dosage regimen reaching the target blood pressure faster than the weight-dependence dosage regimen. Data in PPS was similar to the data in FAS.

In FAS, the survival analysis of the time needed to target blood pressure showed that, the mean time to target blood pressure was 43.42±55.94min and 26.39±30. min (median time 20min (95%CI: 15, 20) and 20min (95%CI: 15, 30)) in control group and study group, respectively. Via Log-Rank test, there was statistical significance between the 2 groups ($P=0.0111$). Data in FAS was consistent as the data in PPS. The survival curve of reaching target blood pressure showed that, patients in study group needed shorter time to reach the target blood pressure. Data in FAS was consistent as the data in PPS.

Safety Result:

In SS, totally 4 patients experienced adverse events (AEs), 2 in each group. Incidence of AE was

2.50%(2/80), same in both groups. During the study period, no serious adverse event (SAE) or death happened in either group. 1 patient in study group discontinued the treatment due to AE.

1 patient in study group (CRFNo.[redacted]) experienced heart rate increasing 15min after administration (severity: suspected or extremely mild). The investigator discontinued the investigational medication. The symptom released 1 hour and 20 minutes later. The investigator judged the relationship between AE and investigational medication “probably”.

Another patient in study group (CRFNo.[redacted]) experienced ALT increasing (48 U/L) 4 hours after administration (severity: suspected or extremely mild). The investigational medication continued with strengthening monitoring. The investigator judged the relationship between AE and investigational medication “probably”. The outcome of this event was failed to obtain.

1 patient in control group (CRFNo.[redacted]) experienced ALT increasing (68 U/L) 25 hours after administration (administration lasted for 5 hours) (severity: suspected or extremely mild). The investigator judged the relationship between AE and investigational medication “very probably”. The investigational medication was discontinued. The outcome of this event was failed to obtain.

Another patient in control group (CRFNo.[redacted]) experienced heart rate increasing 25min after administration (severity: mild). The investigator discontinued the investigational medication with strengthening monitoring. The symptom released after 3 hours and 50 minutes. The investigator judged the relationship between AE and investigational medication “probably”.

In SS, the results of body temperature, heart rate, respiratory rate and blood pressure refer to the table below.

	Baseline value Control group	Baseline value Study group	P value	Change after 48-hour or transfer out of ICU Control group	Change after 48-hour or transfer out of ICU Study group	P value
Body temperature	36.74±0.74	36.66±0.62	0.4854	-0.25±0.70	-0.13±0.48	0.2623

(℃)						
Heart rate (/min)	89.94±23.00	84.04±19.58	0.0834	-8.31±17.50	-2.37±13.87	0.0207
Respiratory rate (/min)	20.78±5.21	20.14±4.90	0.4243	-1.10±5.25	-1.47±4.47	0.6410
SBP (mmHg)	198.99±14.57	198.50±15.76	0.9494	-57.19±22.53	-56.86±19.12	0.9206
DBP (mmHg)	110.44±19.01	110.44±19.01	0.6908	-27.88±16.71	-26.55±16.84	0.6200

For liver and renal function test, most patients stayed normal before and after treatment. In control group, 1 patient's (1.45%) ALT was normal before treatment but clinical significant after treatment. 1 patient's (1.54%) AST was normal before treatment but clinical significant after treatment. In study group, 1 patient's (1.37%) ALT was normal before treatment but clinical significant after treatment.

In SS, ECG results refer to the tables below.

ECG performed (SS)

N(%)	Control Group	Study Group	P value
Total	80(100.00)	80(100.00)	
Performed at baseline	63(78.75)	63(78.75)	1.0000
Performed after administration	39(48.75)	41(51.25)	0.7518

ECG: heart rate (SS)

	Control Group	Study Group	P value
Baseline (/min)			
N (missing)	63(0)	63(0)	
Mean±SD	87.44±21.08	85.11±22.18	0.5461
Median	84.00	80.00	
Q1~Q3	74.00～99.00	71.00～98.00	
IQR	25.00	27.00	
Min~Max	53.00～145.00	51.00～150.00	
95%CI	82.14 ～92.75	79.53～90.70	
After administration (/min)			

ECG: heart rate (SS)

	Control Group	Study Group	P value
N(missing)	39(0)	41(0)	
Mean±SD	83.31±18.37	86.39±19.19	
Median	77.00	84.00	
Q1~Q3	73.00～94.00	75.00～94.00	
IQR	21.00	19.00	
Min~Max	52.00～120.00	57.00～130.00	
95%CI	77.35 ～89.26	80.33 ～92.45	
After administraion – baseline (/min)			
N(missing)	37(0)	39(0)	
Mean±SD	-2.30±15.93	-1.10±10.55	0.4656
Median	-2.00	0.00	
Q1~Q3	-9.00～6.00	-8.00～5.00	
IQR	15.00	13.00	
Min~Max	-45.00～36.00	-28.00～22.00	
95%CI	-7.61 ～3.02	-4.52～2.32	

ECG: sinus rhyme (SS)

N(%)	Control Group	Study Group	P value
Sinus rhyme at baseline	60(95.24)	63(100.00)	0.6114
Sinus rhyme after administraion	38(97.44)	41(100.00)	0.4907

ECG: premature beat (SS)

N(%)	Control Group	Study Group	P value
Premature beat at baseline	4(6.35)	9(14.29)	0.1431
Premature beat after administration	2(5.13)	2(4.88)	1.0000

ECG: ST segment of limb leads (SS)

	Control Group	Study Group	P value
Baseline			**0.5077**
Total	63(100.00)	63(100.00)	
Elevation	1(1.59)	0(0.00)	
No change	21(33.33)	16(25.40)	
Depression	10(15.87)	14(22.22)	
Normal	31(49.21)	33(52.38)	
Inversion	0(0.00)	0(0.00)	
After administraion			**0.5967**
Total	39(100.0)	40(100.00)	
Elevation	0(0.00)	0(0.00)	
No change	18(46.15)	14(35.00)	
Depression	3(7.70)	4(10.00)	

ECG: ST segment of limb leads (SS)

	Control Group	Study Group	P value
Normal	18(46.15)	22(55.00)	
Inversion	0(0.00)	0(0.00)	

ECG: ST segment of chest leads (SS)

	Control Group	Study Group	P value
Baseline			**0.7965**
Total	63(100.00)	63(100.00)	
Elevation	1(1.59)	0(0.00)	
No change	20(31.75)	17(26.98)	
Depression	13(20.63)	14(22.23)	
Normal	28(44.44)	32(50.79)	
Inversion	1(1.59)	0(0.00)	
After administraion			**0.6790**
Total	39(100.00)	40(100.00)	
Elevation	0(0.00)	0(0.00)	
No change	18(46.15)	15(37.50)	
Depression	4(10.26)	6(15.00)	
Normal	17(43.59)	19(47.50)	
Inversion	0(0.00)	0(0.00)	

Above results showed good tolerance and safety profile of the investigational medication. AE rate was 2.50% in both groups, without SAE. For vital signs (respiratory, heart rate, temperature), liver and renal function test, and ECG aspects, there was variety from baseline to after administration in both groups, but within the normal range.

Conclusion:

In this randomized open label study of nicardipine controlling the blood pressure of Chinese hypertensive emergency patients, non weight-dependence dosage adjustment regimen is non-inferior than weight-dependence dosage adjustment regimen which is recommended by SFDA. And non weight-dependence dosage adjustment regimen reaches the target blood pressure faster than weight-dependence dosage adjustment regimen.

Both dosage adjustment regimens are well tolerated without any additional safety concerns, AE rates are both 2.50%, without SAE. Verity of the heart rate before and after administration is minor in both groups, within the normal range.