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Investigation of potential pharmacokinetic interaction between the Fixed-Dose-Combination of perindopril/indapamide/amlodipine compared with Fixed-Dose-Combination of perindopril/indapamide and amlodipine the in healthy Chinese volunteers

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Abstract

S05590 is a fixed-dose combination of perindopril tert-butylamine 4 mg/indapamide 1.25 mg, and S06593 is a fixed-dose combination of perindopril arginine 5 mg/indapamide 1.25 mg/amlodipine 5 mg. The purpose of this study was to determine whether there were pharmacokinetic interactions between the components of S06593, which uses S05590 and amlodipine as reference drugs in Chinese healthy male volunteers after a single oral administration under fasting conditions. Thus, a single-center, open-label, randomized, three-period, six-way crossover study was conducted. A total of 42 subjects were enrolled and randomized to receive S05590 plus amlodipine, or S06593. The doses of perindopril were 3.34 mg in both S05590 and S06593 calculated as free acid. Blood samples were collected in each treatment period to determine the plasma concentrations of perindopril, indapamide, amlodipine, as well as perindoprilat, which is the main metabolite of perindopril. 39 subjects completed this study. The 90% confidence intervals of geometric mean ratios (GMRs) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for perindopril, perindoprilat, indapamide and amlodipine were all within the limits (80.00-125.00 %), indicating that S05590 plus amlodipine and S06593 were pharmacokinetic equivalent. During the study, only one serious emergent adverse event

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(SEAE) was reported, which was considered as not related to study drug by the investigator. And there were no serious treatment-related adverse events in this study.

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1. Introduction

Hypertension, as a major modifiable risk factor for cardiovascular diseases (CVDs), is further heightened in patients with prior cardiovascular events, comorbid diabetes mellitus, microalbuminuria and renal impairment [1,2], and reduction of cardiovascular risks can be achieved by antihypertensive therapy. Angiotensin receptor blockers (ARBs), thiazide diuretics, alpha and beta blockers, calcium antagonists (CCBs) and angiotensin converting enzyme (ACE) inhibitors have been the commonly used classes of antihypertensive agents [2]. However, in more than two-thirds of hypertensive patients, blood pressure (BP) cannot be adequately controlled by monotherapy and requires two or more antihypertensive agents of different classes [3,4]. Available trials have studied different classes of drugs in combination for treatment of hypertension, taking advantage of their complimentary action, and combination therapy is now recommended as first-line treatment in patients with grade 2 or 3 hypertensions or in hypertensive patients with high cardiovascular risk [5]. Thus, the triple-therapy was recommended by the European Society of Cardiology/European Society of Hypertension guidelines [6]. Several studies indicated that three different mechanisms of triple-therapy for the pathogenesis of arterial hypertension are increasingly being used to provide optimal blood pressure control [7-12], with fewer dose-related adverse reactions [13]. The combination of angiotensin II receptor blockers or angiotensin converting enzyme system inhibitors combined with calcium channel blockers and diuretics was recommended in some guidances [14-16].

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Perindopril is an ACE inhibitor approved in all European countries (except in Sweden and in Norway) and other countries for the treatment of hypertension, heart failure and for stable coronary artery disease [17,18], and the ACE inhibitors have also favorable metabolic, renal, cardiovascular and quality-of-life effects as compared with other regimens [19-21]. Indapamide is a thiazide-like chlorosulfamoyl derivative given by oral administration [22]. Indapamide is commonly used in hypertension at a dosage of 2.5 mg (immediate release) and 1.5 mg (slow release) once a day. Amlodipine is a calcium channel blocker, which is mainly used in the treatment of hypertension and angina. Amlodipine was given orally in the form of tablets at doses of 5 or 10 mg once a day [23].

Perindopril, indapamide and amlodipine is one of typical triple-therapy combination. An immediate-release fixed-dose combination (FDC) of perindopril and indapamide (S05590) has been developed in two dosages: perindopril tert-butylamine 2 mg + indapamide 0.625 mg and perindopril tert-butylamine 4 mg + indapamide 1.25 mg. The rationale for FDC of these two active substances is based on their well-demonstrated individual safety and efficacy profiles, their antihypertensive effect over 24 hours, their pharmacodynamic and pharmacokinetic complementary activities and their overlapping properties on risk factors [24-25].

In Europe, perindopril was generally used as tert-butylamine salt at the dosage of 4 to 8 mg (expressed as salt). Recently another formulation of perindopril was registered in Europe and other countries worldwide, including China substituting the tert-butylamine

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salt by a more stable arginine salt at equimolar dosages (5 and 10 mg of perindopril arginine corresponding to 4 and 8 mg of perindopril tert-butylamine, respectively, expressed as salt) [26-28]. S06593 is a new fixed combination of perindopril arginine salt/ indapamide/amlodipine, which is based on the complementary effects of each component on the protection of the hypertensive target organs such as the heart, kidney, brain and vessels (intima-media thickness) in addition to blood pressure reduction [29]. This study is designed to investigate whether there exist pharmacokinetic interactions between the compounds of S06593 in Chinese healthy male volunteers after a single oral administration under fasting conditions.

2. Methods

This clinical trial was registered in chinadrugtrials in 2019 (registration number: CTR20190562) and was conducted during the period of 06/17/2019 to 25/10/2019 at Peking Union Medical College Hospital (PUMCH) in compliance with the clinical study protocol, Good Clinical Practice (GCP), Declaration of Helsinki [30,31], and regulatory requirements. The study protocol and subject informed consent forms (ICF) were approved by the Ethics Committee of PUMCH. Signed hard copies of the ICF were obtained from all subjects prior to their participation in the study. Study drugs S05590, amlodipine and S06593 tablets were supplied by Institut de Recherches Internationales Servier (I.R.I.S.).

2.1 Subjects

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Eligible Chinese healthy male volunteers should be aged between 18 and 50 years (inclusive), with weight between 50-100 kg (inclusive) and a body mass index (BMI) between 19-28 kg/m^2. Prior to enrollment, all subjects were evaluated based on a review of their medical history, physical examination and clinical laboratory examinations. Subjects were excluded if they had a positive result of alcohol/nicotine test, or had used any drugs known to have a hepatic or renal toxicity, or a substance which may inhibit or induce hepatic drug metabolism and/or transport within one month prior to the screening, or had participated in another interventional clinical trial within the 3 months preceding the date when informed consent was given for this study. 42 subjects were allocated to one of the 6 randomly assigned treatment sequences with 7 subjects in each sequence.

Sequence 1: S05590/Amlo/S06593

Sequence 2: S05590/S06593/Amlo

Sequence 3: Amlo/S05590/S06593

Sequence 4: Amlo/S06593/S05590

Sequence 5: S06593/S05590/Amlo

Sequence 6: S06593/Amlo/S05590

During the study, participants were required to abstain from strenuous physical exercise, smoking, and certain products such as alcohol, coffee, tea, cola, chocolate (and other beverages containing xanthine or quinine) and fruit juice.

2.2 Study design

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This study was a single-center, open-label, randomized, three-period, six-way crossover phase I study. The sample size was evaluated based on historical data, which shown that the intra-individual coefficients of variation (CVs%) of C_{max} were up to 26 %, 29%, 18% for indapamide perindopril and amlodipine, respectively [32-36]. Provided an expected theoretical ratio of geometric means of C_{max} and AUC of 1 and relating to an acceptance range of [0.8, 1.25], it has been estimated that at least 38 completed cases were necessary to allow a reasonable chance (power of 90%) for a statistical conclusion of absence of pharmacokinetic interaction between perindopril/indapamide FDC S05590 plus amlodipine within the FDC of perindopril 5 mg/indapamide 1.25 mg/amlodipine 5 mg (S06593) by the assessment of confidence [37].

There were three treatments in this study, namely single oral administration of one tablet of S06593 (FDC of perindopril arginine 5 mg/indapamide 1.25 mg/amlodipine 5 mg), one tablet of S05590 (tert-butylamine 4 mg/indapamide 1.25 mg) and one tablet of amlodipine 5 mg. Each subject underwent three sequential treatment period, namely period 1 (P001), period 2 (P002) and period 3 (P003). For P001, P002 and P003, participants were sequentially randomized to receive one of the above three treatments different from one another with a wash-out time of 3 weeks. A detailed study flowchart is shown in **Figure 1**.

2.3 Safety evaluation

A standard electrocardiogram (12 leads) was performed on the screening day to check that there were no contra-indications and also performed at final visit day to detect the

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onset of any abnormalities (rhythm disorders, conduction disorders or repolarization disorders). Clinical Laboratory tests, including hematology, biochemistry and urinalysis were performed in the central lab on the screening day and final visit day. On the screening day, day1, day 21, day 42 and on the follow-up days vital signs measurements were conducted. All adverse events (AEs) were assessed by investigators for the relationship to the study medications and the severity. All AEs were recorded throughout the study.

2.4 Sample collection

Blood samples were taken for pharmacokinetic (PK) assessment of perindopril, perindoprilat, indapamide and amlodipine prior to treatment administration (pre-dose) and over a period of 240 hours after each treatment administration. Twenty-two blood samples were collected per subject per period, including, pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48, 72, 96, 144, 192, and 240 hours post-dose. Blood samples were collected into labelled lithium heparinized tubes. Centrifugation (10 minutes, 1600 g, +4°C) was performed within 30 minutes after sampling. Then, the plasma was separated into polypropylene tubes and frozen at -30 ± 5° until analysis.

Bioanalytical methods

Plasma concentrations of perindopril, perindoprilat and indapamide were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method in PUMCH [38]. Meanwhile, another LC-MS/MS method was independently developed and validated for amlodipine in Centre for Drug Metabolism and Pharmacokinetics

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Research (DMPK Centre), Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences. The lower limits of analytical quantification (LLOQs) were 0.250 ng/mL for perindopril, perindoprilat and indapamide. While, the lower limit of quantification for amlodipine was 0.0500 ng/mL. These two analytical methods were fully validated for selectivity (no endogenous interference), linearity ($r > 0.995$), intra- and inter-day accuracy and precision, matrix effect, recovery, and calibration curve according to the National Medical Products Administration (NMPA) guidance of bioavailability and bioequivalence study technique for chemistry drug in human [39]. All results met the requirement of the NMPA , the Food and Drug Administration (FDA) , European Medicines Agency (EMA) and International Council of Harmonisation (ICH) [40,43]. All the standard curves and QC samples met their own acceptance criteria defined in the bioanalytical study plans.

2.5 Pharmacokinetic evaluation

A Non-compartmental analysis (NCA) was performed on the individual plasma concentration-time profiles of perindopril, perindoprilat, indapamide and amlodipine obtained for each treatment, using Phoenix™ WinNonlin Version 8.2 (Pharsight Corp., Mountain View, CA, USA). The following PK parameters were calculated and reported for each substance analyzed based on actual sampling times after administration: peak concentration (C_{max}), time at which C_{max} occurred (t_{max}), area under the plasma concentration time curve from 0 to the last quantifiable time point (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$), and terminal half-life ($t_{1/2}$). C_{max} and t_{max} values were presented as

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directly observed data from the plasma concentration time profiles. AUC was calculated using the linear and logarithmic trapezoidal method (linear interpolation in the ascending part of the curve and logarithmic interpolation in the descending part).

2.6 Statistical analysis

Bioequivalence tests were used to compare pharmacokinetic parameters of perindopril, perindoprilat, indapamide and amlodipine administrated as in S05590 or amlodipine 5 mg or in S06593. If bioequivalence criteria were met for each compound when administered in S06593 or administered as S05590 or amlodipine 5 mg, it could be concluded that there was no pharmacokinetic interaction between S05590 and amlodipine 5 mg within S06593.

Bioequivalence was evaluated by comparing PK parameters (C_{max} and AUC_{0-t} (as well as $AUC_{0-\infty}$ if available)) of perindopril, perindoprilat, indapamide and amlodipine after administration of S06593 versus S05590 or amlodipine. Statistical analysis was performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC, USA). Natural log-transformed PK parameters were analyzed with the following linear mixed-effect model using the procedure PROC MIXED with fixed effect for treatment, sequence, period, and a random effect for subject nested in sequence. Geometric mean ratio and its 90% confidence interval (CI) of all above parameters were calculated by the corresponding residual errors followed by inverse-log transformation. The two treatments were considered bioequivalent if the 90% CIs for these parameters were within the range of 80.00%-125.00% [44]. Additionally, as t_{max} cannot conform to a

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normal or lognormal distribution, this parameter was evaluated statistically by Koch's stepwise nonparametric testing procedure. The best nonparametric estimate (Hodges-Lehmann estimate) for the difference of t_{max} between treatments was derived together with a nonparametric confidence interval. The nonparametric test of t_{max} for treatment effects was independent of period.

3. Results

3.1 Subject Disposition and Baseline Characteristics

Overall, 172 subjects were screened for this study. Among them, 44 subjects (2 alternate subjects included) were enrolled and 42 subjects were randomized and allocated to one of the treatment sequences. A total of 39 (92.9%) subjects completed the study. 3 participants (7.1%) were withdrawn from the study: 1 participant at period 1 in the Amlo/S05590/S06593 sequence for AE (anal abscess), 1 participant at period 2 in the S05590/Amlo/S06593 sequence for non-medical reason (unable to continue the medication for personal reasons), 1 participant at period 3 in the S05590/Amlo/S06593 sequence for AE (loss of consciousness).

All subjects (42) received at least one investigational medicinal product (IMP) and were included in the safety set. 42 healthy subjects were included in amlodipine pharmacokinetic analysis after single oral administration of amlodipine. 41 were included in indapamide, perindopril and perindoprilat pharmacokinetic analysis after single oral administration of S05590. And 39 subjects were included in amlodipine,

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indapamide, perindopril and perindoprilat pharmacokinetic analysis after single oral administration of S06593. As planned in the protocol, all participants were Chinese males. They were 20 to 40 years old with a mean ± SD age of 29.0 ± 5.7 years. Healthy volunteers weighed on average 69.30 ± 7.75 kg (ranging from 54.5 to 83.4 kg) and were on average 170.8 ± 6.1 cm tall (ranging from 158 to 184 cm). Their mean BMI was 23.74 ± 2.30 kg/m^2, ranging from 19.4 to 27.9 kg/m^2.

The main demographic data and baseline characteristics were summarized by treatment sequence in **Table 1.** The demographic characteristics in each administration sequence were all balanced.

3.2 Pharmacokinetic evaluation

All pre-dose plasma concentrations of perindopril, perindoprilat, amlodipine and indapamide were below the limit of quantification (BLQ) in this study. After administration of S06593 and S05590, maximum perindopril plasma concentrations were reached at approximately 0.667 h and 0.707 h post-dose in median, respectively. Thereafter, concentrations declined with mean terminal half-lives of 0.689 h and 0.737 h for S06593 and S05590 treatments, respectively.

For the active metabolite, perindoprilat, maximum plasma concentrations were attained in median at 6.46 h and 7.15 h after administration of both S06593 and S05590 treatments. Following the peak of concentration, perindoprilat concentrations then declined in a multi-phasic manner with mean terminal half-lives of 70.0 h and 83.1 h for S06593 and S05590 treatments, respectively.

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Furthermore, maximum indapamide plasma concentrations of S06593 and S05590 treatments were reached at approximately 1.51 h and 1.90 h post-dose in median, respectively. Thereafter, concentrations declined in a multi-phasic manner with mean terminal half-lives of approximately 15.3 h and 15.0 h for both S06593 and S05590 treatments.

Maximum plasma concentrations of amlodipine, were attained at 5.60 h and 5.46 h after administration of S06593 and amlodipine treatments, respectively. Following the peak of concentration, amlodipine concentrations then declined in a multi-phasic manner with mean terminal half-lives of 46.9 h and 45.3 h for both S06593 and amlodipine treatments, respectively.

Descriptive statistics for PK parameters are given in **Table 2** [38]. All results were obtained based on the data of the 42 subjects included for each analyte. The extrapolated part of the $AUC_{0-\infty}$ calculated for perindoprilat accounted for more than 20% of the total $AUC_{0-\infty}$ in 30 subjects for S06593 treatment and in 25 subjects for S05590/amlodipine treatment.

The results show that the mean plasma concentration-time profiles of perindopril, perindoprilat, indapamide and amlodipine were similar following both treatment administrations S05590/amlodipine and S06593. Hence, concentration-time profiles gave no evidence on any differences between these two formulations.

3.3 Statistical analysis

The test treatment in this statistical analysis was S06593, with S05590 and amlodipine

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being the reference. **Table 3** provides the summarized results of GMR and corresponding 90% confidence intervals obtained for the main PK parameters [38].

All S06593/S05590 or S06593/amlodipine GMRs for AUC_{0-t} or $AUC_{0-\infty}$, and C_{max} ranged from 1.04 to 1.13 for perindopril, perindoprilat, indapamide and amlodipine. Furthermore, the 90% confidence intervals were fully contained within the limits of [80.00%-125.00%] for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. Thus, it was indicated that the both treatments were bioequivalent.

Table 4 provides the summarized results of median and 90% confidence interval of perindopril, perindoprilat, indapamide and amlodipine for t_{max} difference. There was generally no appreciable difference in t_{max} of perindopril, perindoprilat, indapamide and amlodipine following administration of S06593 and S05590/amlodipine, with t_{max} difference of -0.00h (-0.55 h, 0.46 h), 0.00h (-3.35 h, 1.96 h), 0.00 h (-2.23 h, 1.45 h) and 0.00 h (-2.74 h, 2.85 h), respectively.

3.4 Safety evaluation

Safety data were collected for all subjects who enrolled in the study. All the reported adverse events occurring on treatment were emergent adverse events (EAEs) including serious adverse events. In the Safety Set, EAEs were reported 26 under S06593, 14 under S05590 and 15 under Amlo and the percentage of participants with at least one EAE was 30.8% under S06593, 26.8% under S05590 and 28.6% under Amlo. The most frequently reported System Organ Class (SOC) involved under each treatment was Cardiac disorders, where 10 participants (25.6%) were affected under S06593, 5

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participants (12.2%) under S05590 and 6 participants (14.3%) under Amlo, mainly due to tachycardia and bradycardia. Tachycardia was reported in 7 participants (17.9 %) under S06593, in 5 participants (12.2%) under S05590 and in 4 participants (9.5%) under Amlo. Most cases of tachycardia were reported as a transient condition happening in standing position without associated signs or symptoms (without reported AE of orthostatic hypotension, except in 1 participant under S06593) and recovered on the same day. Bradycardia was reported in 3 participants (7.7%) under S06593 and 2 participants (4.8%) under Amlo. The event tachycardia was the most frequently reported treatment-related EAE overall (9 participants, 21.4%). No EAE was rated of severe intensity during the study.

Only one serious emergent adverse event was reported during the study. The case of loss of consciousness of moderate intensity, reported in a participant in the S05590/Amlo/S06593 sequence on P3D01 before S06593 administration (thus classified as under Amlo) and considered as not related to study drug by the investigator, was upgraded to serious by the sponsor. The case was upgraded since it belongs to the IME listing. All EAEs in all groups had resolved at the end of the study. **Table 5** shows all the treatment-related EAEs reported throughout the study.

3.5 Vital signs evaluation

Concerning the heart rate (HR), the mean supine HR increased by 7 bpm between study baseline and the end of study visit and the mean standing HR by 5.4 bpm. From the 1st hour post-dosing, the mean supine systolic blood pressure (SBP) and the mean supine

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diastolic blood pressure (DBP) decreased with the 3 treatments, this decrease persisted for at least 24 hours post-dosing (maximum mean decreases in supine SBP: -10.6, -11.0 and -9.7 mmHg at 8 hours post-dosing with S06593, S05590 and Amlo, respectively; maximum mean decreases in supine DBP: -11.6 and -8.3 mmHg at 6 hours post-dosing with S06593 and Amlo, respectively, and -10.2 mmHg at 8 hours post-dosing with S05590). The mean standing SBP and the mean standing DBP decreased from baseline to 24 h post-dosing with the 3 treatments (mean decreases in standing SBP: -7.8, -8.8 and-6.3 mmHg for S06593, S05590 and Amlo, respectively; mean decreases in standing DBP: -5.8, -4.1 and -4.0 mmHg with S06593, S05590 and Amlo, respectively). The mean standing pulse rate increased from baseline to 24 h post-dosing with the 3 treatments, with increases with S06593, S05590 and Amlo of 7.4, 6.0 and 2.8 bpm, respectively.

Lastly, the mean body temperature remained stable from baseline to Day11 with the 3 treatments. The changes in mean standing and supine SBP, DBP and pulse rate were not considered clinically relevant.

4. Discussion

The combinations of different classes of antihypertensive therapies have been developed, taking advantage of their complimentary action [2]. Moreover, FDCs of oral antihypertensive drugs also showed the advantages in simplifying treatment regimens and improving adherence [45]. A couple of studies have demonstrated the

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antihypertensive effectiveness of perindopril/indapamide/amlodipine combination, showing substantially significant reductions in blood pressure and good tolerated [12]. S06593 is a new formulation of perindopril/indapamide/amlodipine combination, resulting from a change of the perindopril salt (from tert-butylamine salt to arginine salt).

In the new FDC (S06593), perindopril is expressed as L-arginine salt which has proved 50% more stable than perindopril-tert-butylamine [27]. At equimolar dosages, the pharmacokinetics, efficacy, safety, and acceptability of the new salt is equivalent to perindopril-tert-butylamine.

Oral administration of S06593 (perindopril arginine salt 5 mg/indapamide 1.25 mg/ amlodipine 5 mg) and S05590 (perindopril tert-butylamine salt 4 mg/indapamide 1.25 mg) or amlodipine 5 mg in healthy Chinese volunteers led to similar mean plasma concentration-time profiles for perindopril, perindoprilat, indapamide and amlodipine. Other bioequivalence study has also shown that there were no drug-drug interactions between perindopril, indapamide and amlodipine when healthy subjects was administrated with the fixed-dose-combination of perindopril/indapamide/amlodipine [46].

For perindoprilat bioequivalence evaluation, some individual values obtained for $AUC_{0-\infty}$ were considered to be unreliable as the percentage of extrapolation of AUC ($AUC\_{\%extrap}$) was higher than 20%. This is explained by the fact that the plasma terminal phase for perindoprilat in plasma which is driven by its dissociation from

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circulating ACE, which is a non-linear and very slow process, making extrapolation of $AUC_{0-\infty}$ not very accurate. This particularity of perindoprilat pharmacokinetics is a general characteristic of ACE inhibitors, which makes their pharmacokinetics fundamentally different from those of conventional drugs [47]. However, lack of $AUC_{0-\infty}$ data is not an issue to conclude to bioequivalence as AUC_{0-t} has been recognized as a reliable parameter for assessing bioequivalence of two oral formulations even better than $AUC_{0-\infty}$ [48].

For t_{max} comparison, this parameter doesn't conform to a normal or lognormal distribution and it was therefore statistically evaluated by Koch's stepwise nonparametric testing procedure. In this study, the Hodges-Lehmann estimate was calculated for the difference of t_{max} between treatments. The results indicated that no appreciable difference in t_{max} of perindopril, perindoprilat, indapamide and amlodipine.

5. Conclusion

The primary objective of this three-period, six-way cross-over, single dose study was to determine whether a PK interaction exists between perindopril tert-butylamine 4 mg (bioequivalent to perindopril arginine 5 mg)/indapamide 1.25 mg fixed combination and amlodipine 5 mg within the fixed combination perindopril arginine 5 mg/indapamide 1.25 mg/amlodipine 5 mg (S06593), after a single oral dose in fasting conditions, in 39 healthy male participants. All the 90% confidence intervals of the GMR of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the range of [80.00% – 125.00%] for perindopril,

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perindoprilat, indapamide and amlodipine. Therefore, it can could be concluded that S06593 and S05590/amlodipine are bioequivalent and there are no pharmacokinetic interactions between S05590 of perindopril tert-butylamine 4 mg/indapamide 1.25 mg and amlodipine 5 mg within the S06593. Safety after single oral administration of S06593 in Chinese healthy male participants is in line with the known safety profile of each of its components.

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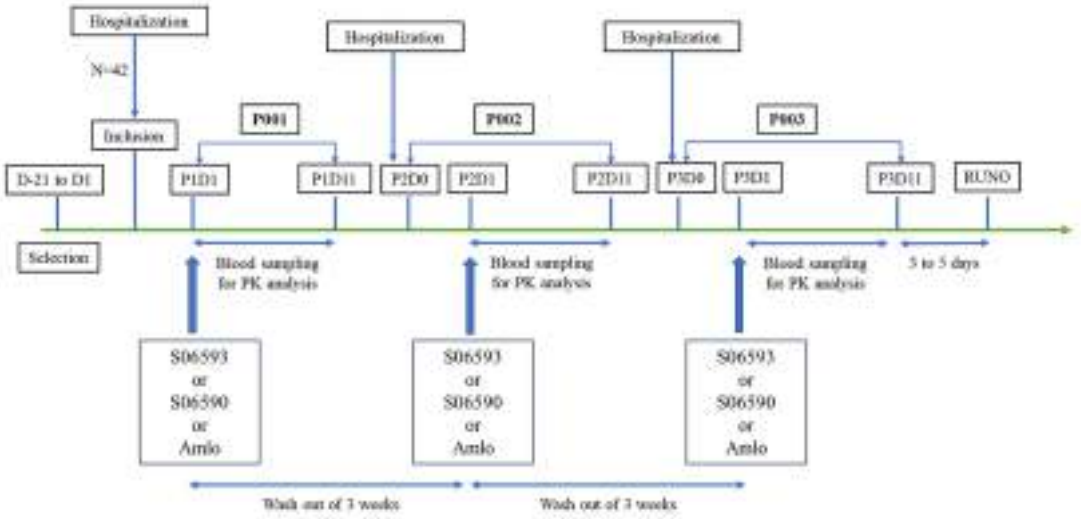

Figure 1 Study Flow Diagram

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Table 1 Main baseline characteristics in the randomized set

Item		S05590/ Amlo/S06593 (N=7)	S05590/ S06593/Amlo (N=7)	Amlo/ S05590/S06593 (N=7)	Amlo/ S06593/S05590 (N=7)	S06593/ S05590/Am (N=7)
Age	n	7	7	7	7	7
(years)	Mean ± SD	32.0 ± 7.8	27.3 ± 5.2	26.7 ± 2.6	31.3 ± 6.1	29.0 ± 6.2
	Median	32.0	26.0	27.0	32.0	27.0
	Min; Max	20; 40	21; 35	23; 30	23; 40	22; 40
Weight	n	7	7	7	7	7
(kg)	Mean ± SD	69.84 ± 10.18	68.71 ± 8.95	69.01 ± 8.77	69.91 ± 4.87	70.41 ± 6.9
	Median	68.80	73.00	64.90	69.00	70.30
	Min; Max	55.9; 81.7	57.5; 78.3	58.0; 83.4	64.1; 76.8	61.3; 79.8
Height	n	7	7	7	7	7
(cm)	Mean ± SD	171.1 ± 7.1	170.1 ± 3.1	173.0 ± 7.5	170.4 ± 2.7	173.6 ± 6.6
	Median	171.0	170.0	176.0	171.0	174.0
	Min; Max	164; 183	165; 174	158; 180	167; 173	166; 184
BMI	n	7	7	7	7	7
(kg/m^2)	Mean ± SD	23.79 ± 2.68	23.71 ± 2.77	23.06 ± 2.45	24.10 ± 1.95	23.39 ± 2.2
	Median	23.70	24.50	23.60	23.90	24.30
	Min; Max	20.4; 27.9	20.5; 27.1	19.4; 25.7	21.4; 27.5	19.6; 25.5

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Table 2 Pharmacokinetic parameters derived from plasma concentration of perindopril, perin

amlodipine after single oral administration of S06593 or S05590/amlodip

Parameters	Units	Amlodipine		Indapamide		Perindopril	
		Amlodipine	S06593	S05590	S06593	S05590	S
$AUC_{\_\%Extrap}$	%	3.63 ± 1.54	3.61 ± 1.52	3.61 ± 1.49	3.37 ± 1.50	1.67 ± 1.05	1.6
$AUC_{0-\infty}$	h*ng/mL	168 ± 50.5	172 ± 45.2	296 ± 53.9	312 ± 65.5	48.0 ± 11.2	50
AUC_{0-t}	h*ng/mL	162 ± 47.2	166 ± 42.5	286 ± 52.3	302 ± 63.9	47.2 ± 11.3	49
C_{max}	ng/mL	3.06 ± 0.702	3.23 ± 0.691	16.6 ± 2.26	18.4 ± 3.88	40.3 ±13.1	43
$T_{1/2}$	h	45.3 ± 8.57	46.9 ±10.4	15.0 ± 2.11	15.3 ± 2.15	0.737 ± 0.151	0.68
T_{max}	h	6.00	6.00	1.50	1.50	0.750	
		(1.50,8.00)	(1.50,8.00)	(0.750,4.00)	(0.750,3.00)	(0.500,1.50)	(0.
T_{lag}	h	0.0774 ± 0.129	0.128±0.139	0.0854 ± 0.120	0.0577±0.107	0.00610±0.0390	0.

Note: Parameters (Excepted T_{max}) were listed with a mean ± SD. T_{max} were listed with median (min,max).

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Table 3 Bioequivalence assessment of perindopril, perindoprilat, indapamide and amlodipine fo

Analysts	Treatment	C_{max}			AUC_{last}			
		Point Estimate	90% CI	Intra-CV	Point Estimate	90% CI	Intra-CV	E
Perindopril	S06593/S05590	1.09	(1.01,1.18)	0.210	1.06	(1.03,1.09)	0.079	
Perindoprilat	S06593/S05590	1.13	(1.06,1.21)	0.181	1.04	(1.00,1.09)	0.109	
Indapamide	S06593/S05590	1.09	(1.04,1.15)	0.139	1.05	(1.00,1.10)	0.121	
Amlodipine	S06593/ **Amlodipine**	1.06	(1.02,1.10)	0.093	1.04	(1.00,1.09)	0.111	

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Table 4 Median and 90% confidence interval of perindopril, perindoprilat, indapamide and am

Parameters	Unite	Amlodipine S06593-Amlodipine	Indapamide S06593-S05590	Perindopril S06593-S0559
Median	h	0.00	0.00	0.00
CI 90%	h	-2.74	-2.23	-0.55
Lower				
CI 90%	h	2.85	1.45	0.46
Upper				

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Table 5 Analysis of treatment-related emergent adverse events by system organ class and prefe

System organ class	S06593 (N=39)			S05590 (N=41)			Amlodipine (N	
Preferred term	NEAE	n	%	NEAE	n	%	NEAE	n
Cardiac disorders	8	7	17.9	5	5	12.2	5	4
Tachycardia	6	6	15.4	5	5	12.2	4	3
Bradycardia	1	1	2.6	-	-	-	1	1
Palpitations	1	1	2.6	-	-	-	-	-
Nervous system disorders	1	1	2.6	-	-	-	2	2
Dizziness	1	1	2.6	-	-	-	-	-
Dizziness postural	-	-	-	-	-	-	1	1
Headache	-	-	-	-	-	-	1	1
Gastrointestinal disorders	2	1	2.6	-	-	-	-	-
Abdominal discomfort	1	1	2.6	-	-	-	-	-
Nausea	1	1	2.6	-	-	-	-	-
General disorders and administration site conditions	1	1	2.6	-	-	-	-	-
Chest discomfort	1	1	2.6	-	-	-	-	-
Vascular disorders	1	1	2.6	-	-	-	-	-
Orthostatic hypotension	1	1	2.6	-	-	-	-	-
Investigations	-	-	-	3	2	4.9	-	-
Alanine aminotransferase increased	-	-	-	1	1	2.4	-	-
Blood pressure decreased	-	-	-	1	1	2.4	-	-
Gamma-glutamyl transferase increased	-	-	-	1	1	2.4	-	-
Respiratory, thoracic and mediastinal disorders		-	-	-	-	-	1	1

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Nasal obstruction		-	-	-	-	-	1	1
ALL	**13**	**7**	**17.9**	**8**	**6**	**14.6**	**8**	**6**

Note: NEAE: Number of treatment-related emergent adverse events.

N: number of participants under treatment

n: number of participants affected

%: n/N * 100