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ORIGINAL RESEARCH

Evaluation of Drug-Drug Interaction Between Henagliflozin and Hydrochlorothiazide in Healthy Chinese Volunteers

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Purpose: Henagliflozin is an original, selective sodium-glucose cotransporter 2 (SGLT2) inhibitor. Hydrochlorothiazide (HCTZ) is a common anti-hypertensive drug. This study aimed to evaluate the potential interaction between henagliflozin and HCTZ.

Methods: This was a single-arm, open-label, multi-dose, three-period study that was conducted in healthy Chinese volunteers. Twelve subjects were treated in three periods, period 1: 25 mg HCTZ for four days, period 2: 10 mg henagliflozin for four days and period 3: 25 mg HCTZ + 10 mg henagliflozin for four days. Blood samples and urine samples were collected before and up to 24 hours after drug administrations on day 4, day 10 and day 14. The plasma concentrations of henagliflozin and HCTZ were analyzed using LC-MS /MS. The urine samples were collected for pharmacodynamic glucose and electrolyte analyses. Tolerability was also evaluated.

Results: The 90% CI of the ratio of geometric means (combination: monotherapy) for $AUC_{\tau,ss}$ of henagliflozin and HCTZ was within the bioequivalence interval of 0.80–1.25. For henagliflozin, co-administration increased $C_{ss,\ max}$ by 24.32% and the 90% CI of the GMR was (108.34%, 142.65%), and the 24-hour urine volume and glucose excretion decreased by 0.43% and 19.6%, respectively. For HCTZ, co-administration decreased $C_{ss,\ max}$ by 19.41% and the 90% CI of the GMR was (71.60%, 90.72%), and the 24-hour urine volume and urinary calcium, potassium, phosphorus, chloride, and sodium excretion decreased by 11.7%, 20.8%, 11.8%, 11.9%, 22.0% and 15.5%, respectively. All subjects (12/12) reported adverse events (AEs), but the majority of theses AEs were mild and no serious AEs were reported.

Conclusion: Although $C_{ss,max}$ was affected by the combination of henagliflozin and HCTZ, there was no clinically meaningful safety interaction between them. Given these results, coadministration of HCTZ should not require any adaptation of henagliflozin dosing.

Trial Registration: ClinicalTrials.gov NCT06083116.

Keywords: henagliflozin, drug-drug interaction, hydrochlorothiazide, pharmacokinetics, tolerability, pharmacodynamics, selective sodium-glucose cotransporter 2

Introduction

Over the past 20 years, the metabolic disease known as type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance and hyperglycemia, has become an epidemic in both industrialized and developing nations. T2DM is a major global health concern.[1] Metformin, a thiazolidinedione insulin sensitizer, sulfonylurea insulin secretagogue, α-glycosidase inhibitors, and other medications with various modes of action are the primary anti-diabetic medications available.[2] Their drawbacks, however, include a limited ability to improve cardiovascular outcomes and, in certain cases, an increase in morbidity associated to cardiovascular disease. Certain medications, like rosiglitazone, pioglitazone, and saxagliptin, have been demonstrated to elevate the likelihood of hospitalization due to heart failure.[3,4] Furthermore, severe hypoglycemia may occur when certain oral hypoglycemic medications are used clinically.[5]

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A new class of medications called sodium-glucose cotransporter 2 (SGLT2) inhibitors is used to treat type 2 diabetes (T2DM). These medications work by preventing the kidneys from reabsorbing glucose, which allows more glucose to be excreted in the urine and lowers blood glucose levels. Clinical research has demonstrated that SGLT2 inhibitors, either taken by alone or in conjunction with other medications, have very potent hypoglycemia effects.[1,6,7] However, investigations on the effects on the kidneys and cardiovascular system have greatly broadened their application. Cardiorenal outcomes trials have proven to be effective in improving renal outcomes and lowering the risk of cardiovascular death, myocardial infarction, hospitalization for heart failure (HHF), and composite major adverse cardiovascular events (MACE) in individuals with type 2 diabetes who have an established or high risk of cardiovascular disease (CVD).[8] Patients with type 2 diabetes who have high risk factors for atherosclerotic cardiovascular disease, heart failure, chronic renal disease, or both should start treating their condition with SGLT2 inhibitors, according to the American Diabetes Association (ADA) and the European Association for Diabetes Studies (EASD).[9–12]

Henagliflozin is a novel SGLT2 inhibitor, which was approved by the National Medical Products Administration (NMPA) of China in 2021. Diabetic patients are often complicated with hypertension.[13,14] HCTZ is recommended as a first-line treatment for hypertension and is also a common ingredient of compound anti-hypertensive drugs.[15,16] Thus, the interaction evaluation of the two drugs can provide guidance for clinical use. The results of this study were used to promote the development of henagliflozin in China by evaluating the drug-drug interaction between henagliflozin and HCTZ using pharmacokinetics, pharmacodynamics, and tolerability assessments.

Materials and Methods

This study was approved by the Independent Ethics Committee (IEC) of Shanghai Xuhui Central Hospital and was carried out in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and other applicable regulatory requirements. All subjects were informed of the study aim, procedures, and risks. Additionally, written consent was obtained from each subject to ensure their voluntary participation in the study.

Subjects

Healthy Chinese male volunteers, 18–40 years of age, with a body mass index between 19 and 26 kg/m^2 were recruited. All volunteers had no clinically significant medical history and normal results for blood chemistry, hematology, urinalysis, vital signs and serology for hepatitis and human immunodeficiency virus (HIV). Four weeks prior to the start of the study, volunteers stopped the use of any medications that could interfere with the procedures or interpretation of data or compromise their safety.

Study Drug

The study used henagliflozin (10 mg/tablet) from Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Lianyungang, China) and HCTZ 25 mg/tablet from Changzhou Pharmaceutical Factory Co., Ltd. in China.

Study Design

This three-period, single-arm, open-label, multi-dose trial was conducted at a single center. After a one-week screening period (day −7 to day −1) to determine subjects' eligibility and baseline evaluation, subjects who passed the test results were checked into Phase I clinical trial wards before the drug administration day (day 1). Twelve subjects received treatment in three periods, period 1: 25 mg HCTZ (day 1 to day 4), period 2: 10 mg henagliflozin for four days (day 7 to day 10) and period 3: 25 mg HCTZ + 10 mg henagliflozin for four days (day 11 to day 14). The study flowchart is presented in Figure 1.

Meals, hydration intake, and the surrounding environment were maintained as consistent and under control as possible both during and in between the periods.

Pharmacokinetic Measurements

To assess the plasma concentrations of henagliflozin and HCTZ, blood samples were taken at 5 min pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post-dose on day 4, day 10 and day 14. Blood samples were also collected to

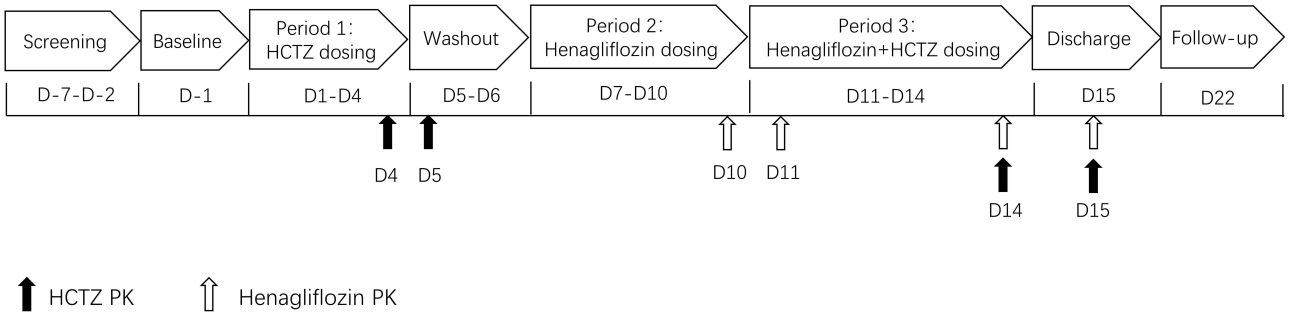

Figure 1 Schematic diagrams of study design.
Abbreviation: HCTZ, hydrochlorothiazide.

determine steady-state blood concentrations for each period (day 2 to day 3, day 8 to day 9 and day 11 to day 13). The collected blood samples were centrifuged at 1500 g for 10 minutes at 4°C within 30 minutes. The separated plasma was stored at −80°C.

Liquid chromatography tandem mass spectrometry (LC-MS/MS) method for determination of henagliflozin and HCTZ levels in human plasma was established and validated. The methodology validation of this method was carried out to assess its selectivity, linearity, precision, accuracy, and stability in solution in accordance with the technical guidelines for clinical pharmacokinetics of chemical drugs published by NMPA.[17] This was done to guarantee the reliability of the method for the determination.

To detect the concentration of henagliflozin and internal standard SHR118597 (analog of henagliflozin), chromatography was performed on a Polaris 3 C18-A column (50×3.0 mm, 3 μm) with a mobile phase containing 0.1% acetic acid water and 0.1% formic acid of acetonitrile/methanol (50/50, volume ratio) mixture by gradient elution at a flow rate of 1.0 mL·min^{-1}. Room temperature was selected for the column. For mass analysis and detection, a Sciex Triple Quad 6500+ mass spectrometer with a TurboIonSpray source (Applied Biosystems, Concord, Ontario, Canada) was employed. Multiple reaction monitoring of the transitions m/z 407.1 → m/z 329.1 for the internal standard (IS) and m/z 453.0 → m/z 321.1 for henagliflozin was used to accomplish MS quantification. The lower limit of quantitation for the plasma was 1 ng/mL and the linear calibration range was 1–500 ng/mL. The accuracy ranged from 94.6% to 113.7% and the interday and intraday precision was < 13%.

To detect the concentration of HCTZ and internal standard Hydrochlorothiazide-^{13}C-d_2, chromatography was performed on a ZORBAX SB-C8 column (50×4.6 mm, 3.5 μm) with a mobile phase containing 5 mM ammonium acetate water and mixed solution of acetonitrile/water (90/10, volume ratio) by gradient elution at a flow rate of 1.0 mL·min-1. A temperature of 40°C was selected for the column. For mass analysis and detection, an API 5000 mass spectrometer fitted with a TurboIonSpray source (Applied Biosystems, Concord, Ontario, Canada) was employed. Multiple reaction monitoring of the transitions m/z 296.0 → m/z 268.9 for HCTZ and m/z 299.0 → m/z 269.9 for IS was used to accomplish MS quantification. The calibration curve was in good linearity with the range of 1 to 400 ng/mL. The accuracy ranged from 89% to 112.5% and the precision of the concentrations determined at each level was less than 7% except at the LLOQ. At the LLOQ, the accuracy was within ±18% and precision was less than 18%.

Pharmacodynamic Measurements

Urine samples were collected for 24 hours after drug administrations on day 4, day 10 and day 14, and the total volume of urine samples was recorded. Moreover, 10 mL of well-mixed urine samples of day 4 and day 14 were absorbed for urine electrolyte testing, while 10 mL of well-mixed urine samples of day 10 and day 14 were absorbed for urine glucose testing.

Statistical Analysis

PK Analysis

The PK parameters were calculated by non-compartmental analysis using WinNonlin 7.0. The PK parameters of henagliflozin and HCTZ in the stages of single administration and co-administration included $C_{ss,max}$ (maximum plasma concentration at steady state), $C_{ss,min}$ (minimum plasma concentration at steady state), $C_{ss,avg}$ (average plasma

concentration at steady state), $AUC_{\tau,ss}$ (area under the curve within a dosing interval (τ) at steady state), $T_{ss,\ max}$ (the time to reach $C_{ss,max}$), $t_{1/2}$ (elimination half-life), $CL_{ss/F}$ (apparent plasma clearance), V_{ss}/F, λ_z (elimination rate constant).

To evaluate the impact of co-administration of HCTZ and henagliflozin on the PK, point estimates and 90% confidence intervals (CIs) were computed for the geometric mean ratios. If the 90% confidence intervals (CIs) for the ratios of population geometric means for henagliflozin + HCTZ to henagliflozin alone were between 0.8 and 1.25 for the $C_{ss,max}$, $AUC_{\tau,ss}$ of henagliflozin, then there was no influence on the PK of henagliflozin. Similarly, if the 90% CIs for the population geometric mean ratios of henagliflozin + HCTZ to HCTZ alone were within 0.80 and 1.25 for the $C_{ss,max}$, $AUC_{\tau,ss}$ of the HCTZ, it was determined that there was no influence on the PK of the HCTZ.

PD Analysis

A descriptive statistical summary of the absolute quantity and the change in co-administration of the 24-hour urine volume and urinary sugar excretion were conducted after henagliflozin was administered alone or with HCTZ. A descriptive statistical summary of the absolute quantity and the change in co-administration of the 24-hour urine volume and urinary electrolyte excretion (sodium, chloride, potassium, calcium, and phosphorus) were conducted after HCTZ was administered alone or with henagliflozin.

Results

Demographic Data

42 volunteers in all were screened. I the end, 12 subjects were enrolled and all of them completed the study. With a mean age (SD) of 28.1 (4.34) years, a mean weight of 66.5 (9.33) kg, a mean height of 168.5 (6.98) cm, and a mean BMI of 23.32 (2.364) kg/m2, all of the subjects were healthy male Chinese volunteers. There were no subject withdrawals from the study. The demographic characteristics of the subjects are summarized in Table 1.

Pharmacokinetics of Henagliflozin

Plasma concentrations of henagliflozin were maintained at a steady state following drug administration either in the monotherapy period (D10) or in the combination (D14) period. The mean plasma henagliflozin concentration–time profiles on days 10 and 14 are shown in Figure 2A. The PK parameters and statistical analyses of the comparison are shown in Table 2. Following medication administration during the combination period, henagliflozin's $AUC_{\tau,ss}$ showed a small rise, and the 90% confidence interval for the geometric mean ratio (combination: monotherapy) fell between 0.80 and 1.25. The GMR of the combination to the henagliflozin alone period for $C_{ss,max}$, had a 90% confidence interval of 124.32% (108.34%, 142.65%), which fell outside the range of 0.80–1.25. The T_{max} of henagliflozin was unaffected by the co-administration of HCTZ. The median (range) T_{max} was 1.75 (1.02–4.00) h without and 1.00 (1.00–4.00) h with co-administration. The CL_{ss}/F and $t_{1/2}$ were similar irrespective of whether henagliflozin was administered alone or with HCTZ.

Pharmacokinetics of Hydrochlorothiazide

Plasma concentrations of HCTZ were maintained at a steady state after drug administration either in the monotherapy period (D4) or in the combination (D14) period. The mean HCTZ plasma concentration-versus time profile with and without co-administration of henagliflozin is shown in Figure 2B. The PK parameters and statistical analyses of the

Table 1 Subjects Demographic Characteristics

Characteristics	Subjects (n=12)
Age (year)	28.1(±4.34)
Height (cm):	168.5(±6.98)
Weight (Kg):	66.5(±9.33)
BMI (kg·m-2)	23.32(±2.364)

Note: Data are presented as Mean ± SD.
Abbreviation: BMI, body mass index.

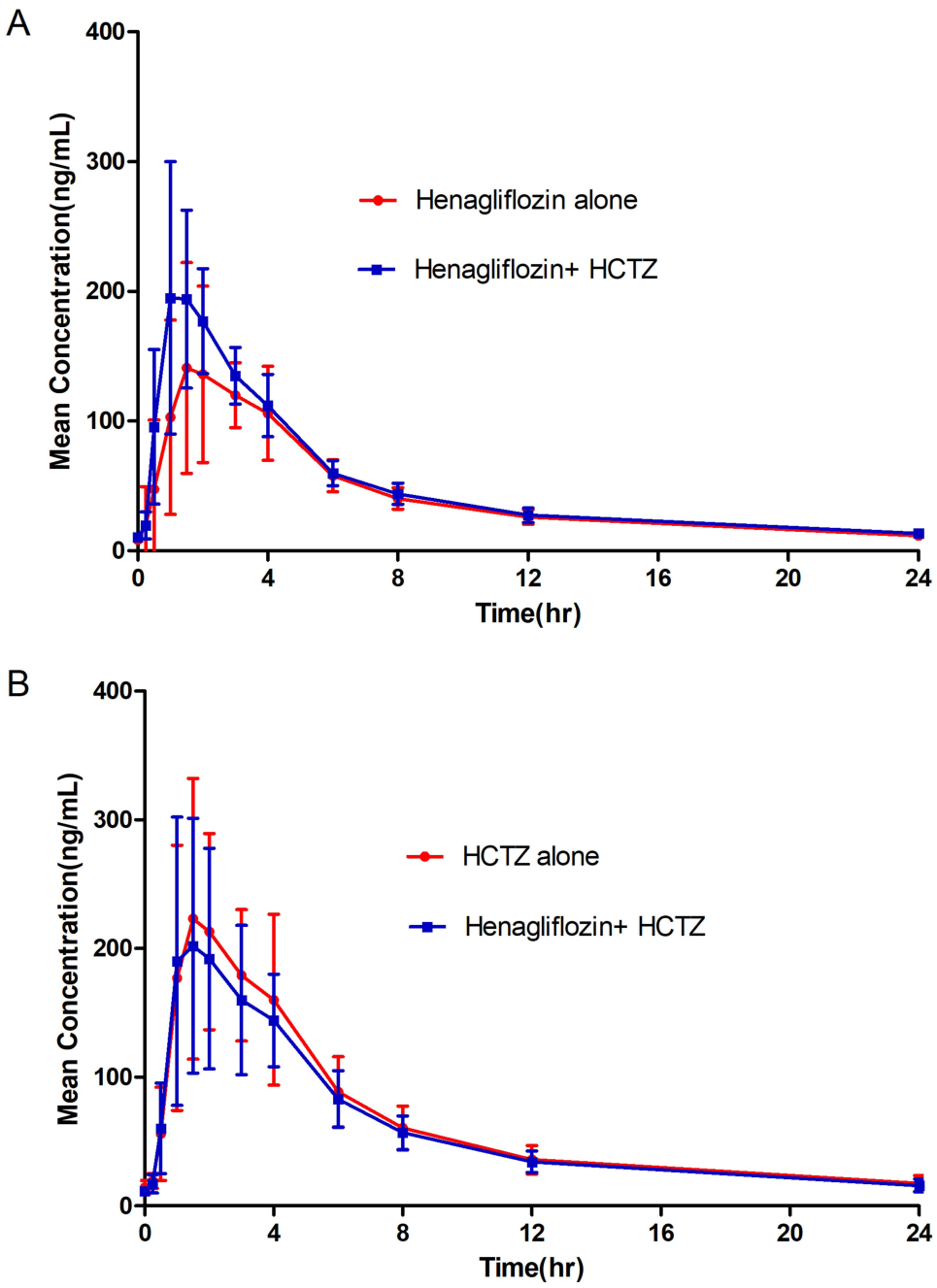

Figure 2 Steady-state plasma concentration–time profiles for (A) henagliflozin and (B) HCTZ following administration of henagliflozin 10 mg once daily or HCTZ 25 mg once daily alone or in combination in healthy subjects.
Note: Data are shown as arithmetic mean ± SD.
Abbreviation: HCTZ, hydrochlorothiazide.

comparison are shown in Table 3. The plasma concentration vs time profile following oral dosing of HCTZ was characterized by a rapid absorption phase, with median T_{max} of 1.5 hours after dose administration, when administered alone or in combination with henagliflozin. The mean $AUC_{\tau,ss}$ for HCTZ was essentially unaffected by co-administration of henagliflozin and the 90% CI of ratio of geometric means ratios (combination: monotherapy) was within the bioequivalence interval of 0.80–1.25. Co-administration of HCTZ with henagliflozin decreased $C_{ss,\ max}$ for HCTZ by 19.41%, and the 90% CI of geometric mean ratios was (71.60, 90.72). The $t_{1/2}$ was slightly decreased with the co-

Table 2 Plasma Pharmacokinetic Parameters of Henagliflozin Following Administration of Henagliflozin 10 Mg Once Daily or in Combination with HCTZ 25 Mg Once Daily in Healthy Subjects

Parameter	GLSM		Ratio of GLSM (%)	90% CI of Ratio (%)
	Henagliflozin	Co-Administration		
$C_{max,ss}$(ng/mL)	171(35.5)	213(33.2)	124.32	(108.34, 142.65)
$AUC_{\tau,ss}$(ng*h/mL)	1010(16.5)	1190(16.7)	117.75	(114.69, 120.90)
T_{max}(h)	1.75(1.02, 4.00)	1.00(1.00, 4.00)		
$t_{1/2}$(h)	9.18±1.01	9.60±0.867		
CL_{ss}/F(L/h)	10.0±1.60	8.52±1.39		

Note: Data are presented as Mean ± SD or number (%).
Abbreviations: GLSM, geometric least-squares mean; CI, confidence interval; $C_{max,ss,}$ the maximum plasma concentration at steady state; $AUC_{\tau,ss}$, the area under the curve within a dosing interval (τ) at steady state; $T_{max,}$ the time to peak plasma concentration; t1/2, elimination half-life; CLss/F, apparent plasma clearance.

Table 3 Plasma Pharmacokinetic Parameters of HCTZ Following Administration of HCTZ 25 Mg Once Daily or in Combination with Henagliflozin 10 Mg Once Daily in Healthy Subjects

Parameter	GLSM		Ratio of GLSM (%)	90 CI of ratio (%)
	HCTZ	Co-Administration		
$C_{max,ss}$(ng/mL)	283±27.6	228±37.1	80.59	(71.60, 90.72)
$AUC_{\tau,ss}$(ng*h/mL)	1500±22.2	1390±24.0	92.63	(85.41, 100.46)
T_{max}(h)	1.50(1.00, 4.00)	1.50(1.00, 4.00)		
$t_{1/2}$(h)	9.22±1.48	8.82±1.00		
CL_{ss}/F(L/h)	17.1±4.01	18.5±4.33		

Note: Data are presented as Mean ± SD or number (%).
Abbreviations: HCTZ, hydrochlorothiazide; GLSM, geometric least-squares mean; CI, confidence interval; $C_{max,ss,}$ the maximum plasma concentration at steady state; $AUC_{\tau,ss}$, the area under the curve within a dosing interval (τ) at steady state; $T_{max,}$ the time to peak plasma concentration; $t_{1/2,}$ elimination half-life; CL_{ss}/F, apparent plasma clearance.

administration of henagliflozin. The CL_{ss}/F showed a similar level when HCTZ was co-administered with henagliflozin compared with HCTZ alone.

Pharmacodynamic Properties

After henagliflozin administration alone and co-administration with HCTZ, the 90% CIs for the least squares mean difference in 24-hour urinary glucose excretion and urine volume were −9.62 (−13.03, −6.20) g and −78.00 mL (2378.65, 222.65) mL, respectively. After HCTZ administration alone and co-administration with henagliflozin, the 90% CIs for the least squares mean difference in 24-hour urinary calcium, urinary potassium, urinary phosphorus, urinary chloride, urinary sodium, and urine volume were 0.13 (−0.11, 0.37) mmol, 10.75 (4.23, 17.27) mmol, 1.88 (−0.49, 4.26) mmol, 25.00 (12.03, 37.97) mmol, 10.75 (−3.01, 24.51) mmol, and 153.67 (−157.47, 464.80) mL, respectively. The Pharmacodynamic analysis of urine are shown in Table 4.

Safety and Tolerability

Treatment emergent AEs (TEAEs) were reported by 100% (12/12) of subjects. The TEAEs included thirst, diarrhea, hypokalemia, dizziness, and eczema. The most common TEAEs were thirst and diarrhea. Except for eczema, which was a moderate AE, all other AEs were mild. All AEs were relatively transient and recovered by the end of the study. No serious AEs were reported. All TEAEs for the study are summarized in Table 5.

During multiple administrations of HCTZ, 26 TEAEs were reported in 11/12 (91.7%) subjects, and 12 TEAEs in 11 subjects were considered to be related to HCTZ. During multiple administrations of henagliflozin, four TEAEs were reported in 4/12 (33.3%) subjects, and all TEAEs were considered to be related to henagliflozin. In the combination

Table 4 Pharmacodynamics Analysis of Urine Volume and Urine Electrolytes Following Administration of Henagliflozin or HCTZ Alone and in Combination in Healthy Subjects

Parameter	Henagliflozin	HCTZ	Co-Administration	LSM	90% CI of LSM
Cumulative urine volume in 24 hours(mL/24h)	2590±565 NA	NA 2360±685	2520±546	−78.00 153.67	−378.65, 222.65 −157.47, 464.80
Urinary glucose excretion(g)	46.5±12.0	NA	36.9±10.3	−9.62	−13.03, −6.20
Urinary calcium excretion (mmol/24h)	NA	2.11±1.27	2.25±1.42	0.13	−0.11, 0.37
Urinary potassium excretion (mmol/24h)	NA	56.8±9.15	67.5±12.7	10.75	4.23, 17.27
Urinary phosphorus excretion (mmol/24h)	NA	22.7±5.78	24.5±5.50	1.88	−0.49, 4.26
Urinary chlorine excretion (mmol/24h)	NA	121±19.0	146±26.7	25.00	12.03, 37.97
Urinary sodium excretion (mmol/24h)	NA	98.2±19.5	109±19.9	10.75	−3.01, 24.51

Note: Data are presented as Mean ± SD or number (%).
Abbreviations: HCTZ, hydrochlorothiazide; LSM, least squares mean; CI, confidence interval; NA, not applicable.

Table 5 Treatment-Emergent Adverse Events and Drug-Related TEAEs After Any Treatment

Types of Adverse Events	HCTZ	Henagliflozin	Co-Administration	Totle
All TEAEs	11(26)	4(4)	5(9)	12(39)
Drug-related TEAEs	11(12)	2(2)	3(3)	12(20)
Thirst	10(10)	0(0)	0(0)	10(10)
Diarrhea	2(2)	2(2)	3(3)	6(7)
Hypokalemia	0(0)	0(0)	1(1)	1(1)
Dizziness	0(0)	1(1)	0(0)	1(1)
Eczema	0(0)	1(1)	0(0)	1(1)

Notes: Data are presented as number (%).
Abbreviations: HCTZ, hydrochlorothiazide; TEAE, treatment emergent adverse event.

period, nine TEAEs were reported in 5/12 (41.7%) subjects. Four TEAEs in four subjects were considered to be related to HCTZ, and three TEAEs in three subjects were considered to be related to henagliflozin.

Discussion

About 70% of patients with type 2 diabetes also have hypertension, and the prevalence of concomitant hypertension and T2DM varies across different ethnic, racial, and social groups.[18] Henagliflozin is an SGLT2 inhibitor created to treat adults with type 2 diabetes by preventing the kidneys from reabsorbing glucose.[19] HCTZ is recommended as a first-line treatment for hypertension. Since both HCTZ and henagliflozin can act on the renal tubules and inhibit the reabsorption of sodium,[20,21] their mechanisms of action and efficacy may influence each other. In the present study, the potential pharmacokinetic and pharmacodynamic interactions, as well as the tolerability of henagliflozin co-administered with HCTZ, were assessed in healthy adults.

According to previous study results, there was no statistical difference in $AUC_{0\text{-}24h}$ and C_{max} between males and females in the 2.5 mg dose group. In the dose range of 1.25 mg to 100 mg, the $AUC_{0\text{-}24h}$ and C_{max} increased with the dose increase at the steady-state (β = 1.0133 and 0.9454, respectively), indicating that the pharmacokinetic behavior of the continuous administration met the linear pharmacokinetic characteristics.[22] Thus, it is speculated that there is also no gender difference in $AUC_{0\text{-}24h}$ and C_{max} in the 10 mg dose group. In order to minimize the impact of individual differences (such as age, weight, and gender) on PK parameters, healthy men aged 18–40 years were selected in this study.

Pharmacokinetic/pharmacodynamic (PK/PD) studies were evaluated in the 5–20 mg dosing range of henagliflozin in healthy subjects and patients with T2DM. The results showed no significant benefit in the 20 mg group compared with the 5 mg and 10 mg groups.[22,23] Therefore, in line with the maximum dose in Phase III clinical trials, 10-mg

henagliflozin dose was chosen in this study. The recommended oral dose for HCTZ is 25–50 mg daily for edematous diseases and 25–100 mg daily for the treatment of hypertension. Combined with the available dose of HCTZ on the market (12.5 mg), 25 mg was selected in this study.

According to the results of previous clinical trials of henagliflozin in healthy subjects and the instructions of hydrochlorothiazide, henagliflozin had an effect on glucose metabolism, while hydrochlorothiazide had an influence on electrolyte and blood volume. 24-hour urinary sugar excretion and urine volume were selected as pharmacodynamic indicators of henagliflozin, and 24-hour urinary electrolyte and urine volume were selected as pharmacodynamic indicators of HCTZ. The pharmacodynamic results showed that henagliflozin had no effect on blood glucose, blood electrolytes, or blood pressure in healthy people,[22] so we only monitored these parameters as a safety assessment. However, the pharmacodynamic effect of HCTZ on the electrolyte balance needs multiple doses to reach a steady state. Thus, HCTZ was given several times in order to investigate the steady state before the combined administration of the two drugs.

Compared to henagliflozin alone, the urine volume decreased by 0.43% in 24 h after co-administration of HCTZ, indicating that co-administration of HCTZ had no significant effect on the urine volume in 24 h. However, the cumulative urinary glucose excretion decreased by 19.6% in 24 h, indicating that cumulative urinary glucose excretion in 24 h was slightly decreased by co-administration of HCTZ.

After co-administration of henagliflozin, the urine volume decreased by 11.3% in 24 h, and the cumulative urinary calcium, urinary potassium, urinary phosphorus, urinary chlorine, and urinary sodium excretion increased by 11.7%, 20.8%, 11.9%, 22.0%, and 15.5% compared to HCTZ alone, respectively, indicating that co-administration of henagliflozin slightly increased 24 h urine volume and the cumulative electrolyte excretion compared to HCTZ alone.

The pharmacokinetic results showed that following concomitant administration of henagliflozin and HCTZ, $C_{ss,max}$ increased by 24.32% compared to henagliflozin alone and decreased by 19.41% than compared to alone, with the 90% CIs for C_{max} slightly exceeding the reference range. The pharmacodynamic results indicated that the glucose excretion in 24 h decreased slightly and the cumulative urinary electrolyte excretion in 24 h increased slightly. However, co-administration of henagliflozin and HCTZ in healthy subjects showed good tolerability. No clinically relevant interaction was observed between henagliflozin and HCTZ from the perspective of safety. The incidence and severity of AEs were in line with those previously reported following the administration of henagliflozin and HCTZ. Under the conditions of this study, safety and tolerability was considered to be good, and no clinically relevant safety interaction was observed between henagliflozin and HCTZ. So coadministration of henagliflozin HCTZ should not require any adaptation of henagliflozin dosing.

The limitations of our study are that only a small number of subjects were enrolled and obtained from healthy male volunteers. The present study cannot be automatically extrapolated to patients with T2DM, especially in individuals treated with several medications or in more fragile patients with hepatic and/or renal impairment. More observation needs to be conduct in further study for the judgment of patients.

Conclusion

Although $C_{ss,max}$ was affected by the combination of henagliflozin and HCTZ, there was no clinically meaningful safety interaction between them. Given these results, coadministration of HCTZ should not require any adaptation of henagliflozin dosing.

Data Sharing Statement

All of the deidentified individual participant data collected during the trial can be shared. The study Protocol, statistical analysis plan and clinical study report can also be available. All shared and available data, besides the information presented in the article, can be obtained by contacting the corresponding author one year after the publication of this study.

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Disclosure

Sheng Feng is a devoted full-time employee of Jiangsu Hengrui Pharmaceuticals Co., Ltd. We would like to state that we have no other conflicts of interest pertaining to the content of this article.

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