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Single Ascending Dose Study to Assess Pharmacokinetic Linearity, Safety, and Tolerability of Trimetazidine - Modified Release in Healthy Human Subjects

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ABSTRACT

Aim This study assessed the linearity of pharmacokinetics (PK) of trimetazidine (TMZ) modified-release tablets (indicated in adults as an add-on therapy for stable angina pectoris) and measured its renal elimination, safety, and tolerability in healthy subjects.

Methods This was a randomized, open-label, single-ascending dose study in healthy subjects. Subjects were administered with a single dose of 35, 70, or 105 mg TMZ-modified release tablets (six subjects each). Pharmacokinetic evaluations and safety analysis were performed before the first dose and till 48 h post-first dose.

Results Following administration of 35, 70, and 105 mg TMZ-modified release; the C_{max} (mean ± SD) was 79.32 (±23.08), 153.17 (±23.08), and 199.67 (±23.08) ng/mL, the T_{max} was 5.42 (±0.49), 4.51 (±1.27), and 4.57 (±0.96) h, $t_{1/2}$ was 7.75 (±1.62), 6.40 (±1.23), and 6.50 (±1.18) h, $AUC_{(0-inf)}$ was 1116.89 (±378.35), 1838.39 (±284.50), and 2504.84 (±348.35) ng.h/mL, CL_R was 13.70 (±2.24), 14.80 (±5.91), and 19.58 (±6.24) $L·h^{-1}$ and CL/F was 33.69 (±8.51), 38.85 (±6.15), and 42.74 (±7.10) $L·h^{-1}$, respectively. Slope estimates for $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max} were less than 1. Corresponding 95% CI of the slope for the AUC parameters excluded 1, indicating that the deviation from dose-proportionality was statistically significant. Corresponding 95% CI of the slope for C_{max} included 1, indicating that the less than dose-proportional increase in C_{max} was not statistically significant. No significant adverse events were observed.

Conclusion Substantial deviation from a dose-proportional increase in $AUC_{(0-inf)}$ and $AUC_{(0-t)}$ suggested a non-linear PK for TMZ-modified release. Single dose of TMZ-modified release was well tolerated and safe.

Introduction

Trimetazidine (TMZ), an anti-ischemic and anti-anginal metabolic agent, is indicated in adults as an add-on therapy for the sympto-

matic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies. Its modified release (MR) tablet is recommended as TMZ

35 mg tablet to administer twice daily. The pharmacokinetics (PK) of TMZ is described in the product labeling [1]. Elimination of TMZ has been found to be predominantly renal with 79–84% of administered radioactivity appearing in the urine within 24 h, of which at least 60% was due to unchanged TMZ [2]. Yet, there is limited knowledge on the PK of TMZ in both the elderly and in subjects with renal function impairment. The effect of age and renal function on the PK profile of the modified release (MR) tablet of TMZ 35 mg administered twice daily has been studied previously [3]. TMZ renal clearance was approximately 25.2 L/h (420 mL min^{-1}) in subjects with normal renal function, 3.5-fold higher than the glomerular filtration rate (GFR). The high renal clearance as a result of the relatively low plasma protein binding of TMZ (15%) suggests a significant renal tubular secretion. Moreover, it has been observed that stable angina pectoris, for which TMZ is indicated, is more frequent in the elderly and impaired kidney function patients. Given the role of the kidneys in the pharmacokinetics (PK) and specifically the clearance of TMZ, further evaluation of the target population for TMZ, *i.e.,* elderly and patients with impaired kidney function, is needed for any potential dosing adjustment [3, 4].

In 2011, TMZ was subjected to an Article 31 Referral procedure in Europe, initiated by the French Health products Agency (AFS-SAPS, now ANSM) at the European Medicines agency (EMA) due to both efficacy and safety concerns (including Parkinson's syndrome and lack of data in frail target populations) [5]. After the review, the Committee for Medicinal Products for Human Use (CHMP) requested that "The MAH should perform a PK study assessing the effect of renal impairment and age on TMZ PK according to the CHMP agreed protocol" as data were lacking in these subject groups because the elderly (above 65 and even 75 years of age) were an important target population for treatment with TMZ. However, the linearity of PK of trimetazidine had not been established. Thus, as a first step we conducted the current single ascending dose study to assess linearity of PK of trimetazidine. We conducted this study in healthy subjects with various dosage regimen to assess linearity of PK of TMZ-modified release. Based on the results of current study, we also conducted a multiple-dose to evaluate the effect of age and renal impairment on the pharmacokinetics of trimetazidine (TMZ) in healthy elderly and renally-impaired subjects and to assess its safety and tolerability profile. Results of the multiple-dose study have been published elsewhere[6].

Therefore, the current study was conducted in accordance with the CHMP requirements to evaluate PK and safety of TMZ. Specifically, the objectives of this study were to assess: (1) linearity of PK of TMZ-modified release, and (2) the safety and tolerability of TMZ in healthy subjects.

Methods

Study Design

This was a randomized, open-label, single ascending-dose study. Eighteen healthy subjects of any gender of 18–55 years of age with normal renal function were enrolled. Subjects were screened within 2 months of admission. Sample size was determined based on 'the evaluation of the 'Pharmacokinetics of medicinal products in patients with decreased renal function EMA/83874/2014.' Subjects were included in this study if they had no clinically relevant abnormalities identified by a detailed medical history, full physical examination, blood pressure (BP), pulse measurements, temperature, respiratory rate (RR), height, weight, 12-lead electrocardiogram (ECG), and clinical laboratory tests. Subjects were excluded from the study if they had a condition that could be affected by participation in the study or by administration of TMZ-modified release or might interfere with the interpretation of the study. Subjects with hypersensitivity to TMZ, excipients, any structurally related drugs and/or any excipient were also excluded. No concomitant medications were allowed during the study, except for hormone replacement therapy and/or paracetamol (up to 1 g/day for analgesia). The eligibility status of the participants was reconfirmed on the day before the study. This joint study was sponsored by a consortium of TMZ Marketing Authorization Holders in the European Union. All study procedures were conducted in accordance with the ethical principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. An Independent Ethics Committee reviewed and approved the study protocol and informed consent form before participants were screened. All participants provided written informed consent before admission to the study.

Intervention and posology

The 18 study subjects were randomly assigned to 3 parallel cohorts of 6 subjects each to receive a single ascending dose of 35, 70 mg or 105 of oral TMZ-modified release tablet. According to SmPC (summary of product characteristics) for trimetazidine, the normal dose for trimetazidine for adult is 35 mg twice a day. Based on this standard dosing, we selected these single doses. The study medication was provided as the branded Moduxin® MR 35 mg, retard tablet (manufactured by Gedeon Richter, Romania). The tablets were administered orally at scheduled dosing time in sitting position with 240 mL of drinking water and standard breakfast (single dosing).

Pharmacokinetic evaluation

Blood samples (4 mL) were collected before dosing and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 36, and 48 h after dosing. Drug administration and blood sampling processes were under continuous medical supervision. Collected blood samples were centrifuged at 3000 g for 10 min. The plasma was separated and stored at approximately −20 °C for further analysis. Quantification of trimetazidine in plasma samples was carried out using analytical assay method of High-Performance Liquid Chromatography (HPLC) with Tandem Mass Spectrometer (MS/MS) detection which was developed and validated before the start of the clinical study. This method was developed for a concentration range spanning the TMZ levels from 4.8 – 28.0 μg/mL which was expected to be present in the plasma samples collected during the clinical study. Blood and urine samples were also analysed in central laboratory to measure clinical laboratory parameters.

The pharmacokinetic parameters of TMZ were calculated by non-compartmental analysis methods using Phoenix® WinNonlin® software, version 6.3. Actual sampling times relative to dosing rather than nominal times were used in the calculation of all derived PK parameters. There was no imputation of missing data. Pharmacokinetic parameters evaluated were: area under the plasma concen-

tration-time curve from time 0 to the last quantifiable concentration ($AUC_{(0-t)}$), area under the plasma concentration-time curve from time 0 to ∞ was calculated as $AUC_{(0-inf)} = AUC_{(0-t)} + C_{last}/\lambda_z$, where C_{last} was the last quantifiable plasma concentration and λ_z was the apparent terminal elimination rate constant ($AUC_{(0-inf)}$), apparent total body clearance (CL/F) and maximum observed plasma concentration (C_{max}) were used for the assessment of linearity. Secondary endpoints included the renal elimination of TMZ (renal clearance [CL_R]) and safety parameters. Pharmacokinetic concentration data were listed by subject including actual sampling times relative to dosing. Plasma and urine concentrations were analyzed by analyte (TMZ), intervention group/cohort, and nominal time point. Descriptive statistics of PK parameters for plasma concentrations obtained at each nominal time point were summarized by intervention group/cohort. Coefficient of variation (CV %), and geometric CV % (calculated as: $gCV\% = SQRT[exp(SD^2)-1] * 100$; where SD = standard deviation of the natural-logarithmically-transformed data) values were calculated. Mean plasma concentrations versus nominal times were also presented in a linear and semi-logarithmic scale. To confirm renal function in these healthy subjects, renal function was assessed by estimating creatinine clearance (from serum creatinine [Scr]) using the Modification of Diet in Renal Disease (MDRD) approach, prior to enrollment or screening period [7].

The MDRD formula was:

eGFR (mL/min/1.73 m²) = 175 × (Scr, std) $^{-1.154}$ (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

Assessment of Dose-Proportionality

Dose-proportionality was assessed for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ using the following power model:

$$\ln <Parameter> = \alpha + \beta \ln <Dose>$$
When both sides are exponentiated:

$$<Parameter> = \exp(\alpha) \cdot <Dose>^\beta$$
Thus, when β = 1, the drug is proportional.

Actual and planned dose values were used in the analyses. The parameter estimates for β and 95 % confidence interval were presented to assess dose-proportionality. No inferential analysis was performed other than the dose-proportionality analysis.

Safety evaluation

Numbers of Treatment-emergent adverse events (TEAEs) were summarized by System Organ Class (SOC) and preferred term and severity/causality to the study drug. The following safety variables were assessed: physical examination, vital signs (BP, pulse, oral temperature, respiratory rate (RR) measured in breaths per minute, 12-lead ECG in triplicate, haematology (red blood cell count, mean corpuscular volume [MCV]), mean corpuscular haemoglobin, haemoglobin, haematocrit, platelet count, white blood cell count and differentials (neutrophils, eosinophils, basophils, lymphocytes, monocytes), biochemistry (magnesium, sodium, potassium, chloride, creatinine, creatine phosphokinase, glucose, urea, uric acid, calcium, inorganic phosphorus, alkaline phosphatase [AP], Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], gamma-glutamyl transferase, total bilirubin, total protein, albumin,

total cholesterol and triglycerides), and urine analysis. A midstream, clean-catch urine specimen was collected for dipstick analysis of bilirubin, protein, blood, glucose, nitrite, ketone, and pH. Urine samples positive for blood or protein, were sent for microscopy if deemed appropriate by the investigator. Pregnancy, adverse events (AEs), and QTc interval were also recorded. The grading and reporting of AE were performed according to Common Terminology Criteria for Adverse Events (CTCAE).

Results

Demographics

Of the 51 subjects who were screened in the study, 18 subjects met all the study eligibility criteria and completed treatment and follow-up (▶ **Table 1**). Most of the subjects in the study were female (72.2 %), Caucasian (94.4 %) and aged between 19 and 51 years. In the 35-mg dose group, all the subjects were females.

TMZ pharmacokinetic analysis

The arithmetic mean maximum plasma concentration (C_{max}) of TMZ-modified release following a single-dose of 35, 70, and 105 mg was 79.32 (± 23.08), 153.172 (± 23.08), and 199.677 (± 23.08) ng/mL, respectively (▶ **Fig. 1**). The corresponding median time to C_{max} (T_{max}) was comparable across the dose range investigated [5.42 (± 0.49), 4.51 (± 1.27), and 4.57 (± 0.96), respectively] (▶ **Table 2**).

▶ **Table 1** Subject demographics.

Parameter	Intervention group			Total
	35 mg (n = 6)	70 mg (n = 6)	105 mg (n = 6)	N = 18
Age (years)				
Mean (± SD)	38.5 (± 12.39)	29.2 (± 8.91)	34.8 (± 11.05)	34.2 (± 10.96)
Gender				
Male	0	2 (33.3 %)	3 (50.0 %)	5 (27.8 %)
Female	6 (100 %)	4 (66.7 %)	3 (50.0 %)	13 (72.2 %)
Race				
Caucasian	6 (100 %)	5 (83.3 %)	6 (100 %)	17 (94.4 %)
American Indian or Alaska Native	0	1 (16.7 %)	0	1 (5.6 %)
Height (cm)				
Mean (± SD)	163.2 (± 4.26)	167.5 (± 13.37)	177.5 (± 10.48)	169.4 (± 11.33)
Weight (kg)				
Mean (± SD)	60.18 (± 6.1)	61.35 (± 12.68)	73.50 (± 14.27)	65.01 (± 12.51)
BMI (kg·m^{-2})				
Mean (± SD)	22.57 (± 1.64)	21.68 (± 1.98)	23.13 (± 2.69)	22.46 (± 2.11)
Serum Creatinine (mg·L^{-1})				
Mean (± SD)	57.00 (± 7.3)	62.62 (± 9.93)	64.70 (± 8.81)	61.44 (± 8.87)

Abbreviation: N = total number of enrolled subjects; n = number of subjects in each group; SD = Standard Deviation.
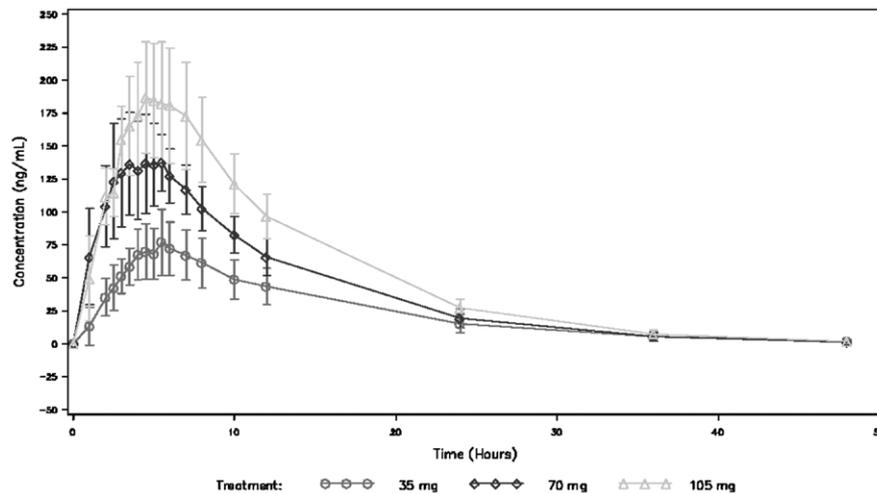
> **Fig. 1** Trimetazidine plasma concentration (mean ± SD) vs. time profile following administration of 35, 70, or 105 mg trimetazidine to healthy subjects (linear scale). Assessment of linearity.

> **Table 2** Summary of pharmacokinetic parameters following administration of 35, 70 or 105 mg trimetazidine to healthy subjects (N = 18) mean (± SD).

PK Parameter	35 mg (n = 6)	70 mg (n = 6)	105 mg (n = 6)
C_{max} (ng mL^{-1})	79.32 (± 23.08)	153.17 (± 32.53)	199.67 (± 42.5)
T_{max} (h)	5.42 (± 0.49)	4.51 (± 1.27)	4.57 (± 0.96)
$t_{1/2}$ (h)	7.75 (± 1.62)	6.40 (± 1.23)	6.50 (± 1.18)
$AUC_{(0-t)}$ (ng.h mL^{-1})	1090.09 (± 353.01)	1822.18 (± 278.57)	2480.80 (± 345.88)
$AUC_{(0-inf)}$ (ng.h mL^{-1})	1116.89 (± 378.35)	1838.59 (± 284.50)	2504.84 (± 348.35)
CL/F (L·h^{-1})	33.69 (± 8.51)	38.85 (± 6.15)	42.74 (± 7.10)
CL_R (L·h^{-1})	13.70 (± 2.24)	14.80 (± 5.91)	19.58 (± 6.24)

Abbreviation: AUC = Area under the curve; N = total number of subjects; SD = standard deviation, n = number of subjects in the group.

> **Table 3** Statistical analysis of trimetazidine pharmacokinetic parameters for the assessment of linearity (slope estimate and 95 % CI) (N = 18).

PK parameter	Slope estimate (β) (95 % CI)
$AUC_{(0-inf)}$ (ng.h mL^{-1})	0.76 (0.54, 0.99)
$AUC_{(0-t)}$ (ng.h mL^{-1})	0.77 (0.56, 0.99)
C_{max} (ng mL^{-1})	0.87 (0.60, 1.13)

Dose Range = 35 mg (n = 6), 70 mg (n = 6), and 105 mg (n = 6); Abbreviation: AUC = Area Under the Curve; CI = Confidence Interval

ating that a less than dose-proportional increase in systemic exposure was observed with increasing dose (▶ **Table 3**). The corresponding 95 % CI of the slope for the AUC parameters excluded 1, indicating that the deviation from dose-proportionality is statistically significant. Conversely, the corresponding 95 % CI of the slope for C_{max} included 1, indicating that the less than dose-proportional increase in C_{max} was not statistically significant. Taken together, these results showed a non-linear PK for a single ascending dose of TMZ in healthy subjects.

Safety results

There was no notable change in biochemistry and hematology parameters of the subjects in the study (data not shown). Changes in vital signs from screening were small and there were no differences among the groups in the study (data not shown). There were no clinically significant changes from screening for any subject in the study with respect to ECG findings (data not shown). Overall, the incidence of treatment-emergent adverse events (TEAE) was low. Among the 18 subjects in the study, 7 subjects (38.9 %) experienced a total of 10 AEs during the study. Of these 10 AEs, 9 were TEAEs. All TEAEs reported were mild. Three of the nine TEAEs were considered related to the study drug by the investigator and all TEAEs were resolved (▶ **Table 4**). The most common TEAE reported in the study was oral herpes (infections and infestations SOC, two subjects). Three TEAEs (upper abdominal pain, headache, and agita-

Following attainment of C_{max}, the plasma concentration-time profile declined in a broadly mono-exponential fashion with a mean $t_{1/2}$ which was similar in each of the dose groups ranging from 6.40 to 7.75 h. An increase in total exposure ($AUC_{(0-inf)}$) [1116.897 (± 378.35), 1838.39 (± 284.50), and 2504.845 (± 348.35) ng.h mL^{-1}, respectively] was observed with increasing dose. CL_R was increased in an apparently dose-dependent manner [3.70 (± 2.24), 14.80 (± 5.91), and 19.58 (± 6.24) L·h^{-1}, respectively] (▶ **Table 2**). A concomitant increase in the apparent CL following oral administration (CL/F) was also observed [33.69 (± 8.51), 38.85 (± 6.15), and 42.74 (± 7.10) L·h^{-1}, respectively].

Effect of a single dose (35, 70, and 105 mg) of TMZ-modified release on the PK parameters $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max} was analyzed. The slope estimates for all three parameters were less than 1, indic-

▶ **Table 4** Treatment-emergent adverse events by system organ class, preferred term, and causality by groups (N = 18).

System Organ Class Preferred Term	Causality	35 mg (n = 6) n (%), #E	70 mg (n = 6) n (%), #E	105 mg (n = 6) n (%), #E
Gastrointestinal disorders				
Abdominal pain (upper)	Related	1 (16.7 %), 1	0	0
General disorders and administration site conditions				
Injection site pain	Not related	0	0	1 (16.7 %), 1
Infections and infestations				
Oral herpes	Not related	1 (16.7 %), 1	0	1 (16.7 %), 1
Nervous system disorders				
Headache	Related	0	0	1 (16.7 %), 1
Sciatica	Not related	0	1 (16.7 %) 1	0
Psychiatric disorders				
Agitation	Related	1 (16.7 %), 1	0	0
Respiratory, thoracic, and mediastinal disorders				
Cough	Not related	0	0	1 (16.7 %), 1
Oropharyngeal pain	Not related	0	1 (16.7 %), 1	0
Abbreviations: N = total number of subjects in safety analysis Set; n = number of subjects; #E = number of events.				

tion) in three subjects were considered related to study drug by the investigator in the study. During the study, no fatal outcomes were observed. There were no severe and no serious adverse event (SAEs) reported in the study. No subject discontinued due to AE from the study. Thus, single-dosing of 35, 70, and 105 mg strengths of TMZ-modified release was well-tolerated by the healthy subjects in the study.

Discussion

In this single ascending dose study, pharmacokinetic parameters after administration of 35 mg, 70 mg, and 105 mg TMZ-modified release were evaluated in healthy subjects. A less than dose-proportional increase in $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max} was noted. A dose-dependent increase in CL_R and CL/F after single dose administration was observed. Statistical analysis of linearity confirmed that the less than dose-proportional increase in $AUC_{(0-inf)}$ and $AUC_{(0-t)}$ was significant, indicating that the pharmacokinetics of TMZ-modified release is dose dependent over the range of 35 to 105 mg. It may be due to an increase in CL_R with increasing dose. Taken together, our results suggest that TMZ-modified release follow a non-linear pharmacokinetics in human subjects. In addition, the TMZ-modified release was well tolerated in all dose groups. No new or unexpected safety concerns were identified during the study.

To our knowledge, this is the first single ascending dose to evaluate the PK of TMZ-modified release in healthy subjects. No phase I study has been performed for TMZ-modified release which determined the linearity of TMZ-modified release after the single ascending dose. However, a few investigators have reported different PK characteristics of TMZ-modified release. In this study, mean C_{max} of 79.32 (± 23.08) ng mL^{-1} was observed with a single dose of 35 mg TMZ-modified release. This result is in line with a previous study by Ozbay *et al* that reported a median C_{max} of 63.1 (± 17.1) ng mL^{-1} with TMZ [8]. In addition, the median T_{max} of 5 h reported previously in healthy subjects taking TMZ-modified release (35 mg) is similar to results obtained in our study (5.42 h) [8]. Moreover, the

mean $AUC_{(0-inf)}$ reported in this study was 1116.89 (± 378.35) ng.h mL^{-1} as compared to 793.4 (± 249.0) ng.h mL^{-1} reported by others [8]. In addition, total body clearance of TMZ in this study [33.69 (± 8.51) L·h^{-1}] was found comparable to other studies [25.2 (± 4.5) L h^{-1}] [3]. Of note, the comparison of the study results to other studies should be done with caution due to the differences in study designs and/or subject demographics.

A few clinical trials have evaluated the safety profile of TMZ in humans. However, for the first time, we conducted a single ascending dose study that included a dose of 105 mg, three times more than the recommended dose. No SAE, death or discontinuation due to AEs was observed at any dose in this study, suggesting that a single dose of TMZ-modified release is well tolerated in healthy subjects, even at a dose three times higher than the recommended dose. Only a few TEAE were observed in this study which were mild to moderate in nature and in line with other published studies [9]. Only one case of each of upper abdominal pain, headache, and agitation in three subjects was observed. These AE were considered related to study drug by the investigator. However, in other studies gastric or esophageal burning, muscular cramps, dizziness, effort induced discomfort, depression, sedation, and/or drowsiness, palpitations, visual disturbances, anorexia and hyperorexia have been reported more frequently. TMZ has also been shown to induce parkinsonism, gait disorders and tremor as well. However, the benefits of TMZ therapy continue to outweigh the risks in patients with angina pectoris [5]. Few study limitations should be mentioned. The study was designed as an open-label study rather than a blind placebo-controlled trial. Moreover, the study was conducted with a single-dose and was also limited by the small sample size. Therefore, interpretations of treatment-related AEs should keep this study design in mind.

Only 6 subjects were recruited for each dose regimen. Thus, individual differences in PK parameters may have led to non-linear PK. However, we have taken the blood samples for measurement of PK parameters at short time intervals and included only healthy subjects. We believe these two factors mitigated the effect of small

sample size. Moreover, it was a single ascending dose study to assess the linearity of PK of trimetazidine in accordance with the standard guidelines which suggest a small sample size for single ascending dose study. A detailed population pharmacokinetic analysis can be performed using the data obtained from this study to assess effect of individual differences and small sample size. However, it is beyond the scope of this study. Furthermore, number of females was not similar among all three groups (50 – 100 %). AUC could be different for male and female and could be a reason for the less than dose-proportional increase in $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max}. Of note, all subjects in the 35 mg treatment group were female which might be a reason for higher $AUC_{(0-inf)}$, $AUC_{(0-t)}$, and C_{max} in this group. However, it has been reported that gender does not affect clinical efficacy of trimetazidine [10]. In addition, it has also been reported in the literature that except for a few drugs, gender-related difference in the pharmacokinetics does not lead to significant effect on clinical efficacy of the drugs [11]. Furthermore, this study was designed according to standard guidelines for PK studies. Therefore, we did not perform any sub-group analysis in this study including effect of gender difference among various dose groups on the linearity of PK of trimetazidine.

Conclusions

Results of this study fills the gap in the data regarding PK parameters of TMZ-modified release. Our results showed a non-linear PK of TMZ-modified release in human subjects. In addition, it was well-tolerated, and no major safety issue was reported. Hence, our study provides adequate preliminary data on dose, safety, and tolerability of TMZ-modified release. The CHMP has requested to conduct pharmacokinetic study in special population including elderly and renal-impaired patients. However, clinical trial data on the linearity of PK of trimetazidine was not available. Thus, as a first step, we conducted the current study to assess linearity of PK of trimetazidine in healthy subjects. Since results from this study showed a non-linear PK of trimetazidine, we designed another multiple-dose study evaluating 'effect of age and glomerular filtration rate on the pharmacokinetics and safety of trimetazidine. Results from the multiple-dose dose study have been published elsewhere.

Disclosures

Acknowledgement

Conflict of Interest

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