Clinical Study Report Synopsis	
Drug Substance	Zibotentan
Study Code	D4326C00001
Edition Number	Final 1.0
Date	02 June 2022
EudraCT Number	2021-003289-10
NCT Number	Not applicable

A Single-dose, Non-Randomised, Open-Label, Parallel-Group Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Zibotentan in Healthy Participants compared to Participants with Moderate Hepatic and Moderate Renal Impairment

Study dates: First participant enrolled: 10 November 2021
Last participant last visit: 15 December 2021
The analyses presented in this report are based on a database lock date of 18 March 2022

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Study Centre

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Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the PK of a single oral dose of zibotentan in subjects with moderate hepatic impairment and moderate renal impairment compared to a group of healthy matched controls	Pharmacokinetic parameters for Day 1 through 120 hours: • AUCinf • AUClast • Cmax
Secondary	
• To evaluate the safety and tolerability of a single oral dose of zibotentan in subjects with moderate hepatic impairment and moderate renal impairment compared to a group of healthy matched controls	• Treatment emergent AEs up to the final safety assessment • Routine safety assessments up to the final safety assessment • Safety laboratory analysis up to the final safety assessment
• To further characterise zibotentan plasma PK in all treatment groups	Pharmacokinetic parameters for Day 1 through 120 hours: • tmax • AUC(0-24) and AUC(0-72) • C24 • t½λz • λz • CL/F • CLNR/F • Vz/F
• To characterise zibotentan urine PK in all treatment groups	Pharmacokinetic parameters for Day 1 through 72 hours: • Ae (by time point and cumulative) • fe (by time point and cumulative) • CLR

Objectives	Endpoints
Tertiary/Exploratory	
• CCI [redacted]	CCI [redacted]

Abbreviations: Ae = amount of unchanged drug excreted into urine; AE = adverse event; CCI [redacted]; AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 hours post-dose; AUC(0-72) = area under plasma concentration-time curve from time zero to 72 hours post-dose; AUCinf = area under plasma concentration-time curve from zero to infinity; AUClast = area under the plasma concentration-curve from time zero to time of last quantifiable concentration; C24 = concentration at 24 hours post-dose; CL/F = apparent total body clearance of drug from plasma after extravascular administration; CLNR/F = apparent total non-renal body clearance of drug from plasma after extravascular administration; CLR = renal clearance of drug from plasma, calculated as Ae0-t/AUC0-t where t is matched for urine and plasma; Cmax = maximum plasma drug concentration; CSR = clinical study report; fe = percentage of dose excreted unchanged in urine; λz = terminal elimination rate constant; PK = pharmacokinetic(s); t½λz = half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; tmax = time to reach maximum observed plasma concentration; Vz/F = apparent volume of distribution during the terminal phase after extravascular administration.

Study Design

This was a single-dose, non-randomised, open-label, parallel-group study to examine the pharmacokinetic (PK), safety, and tolerability of zibotentan in participants with moderate hepatic impairment and moderate renal impairment compared to a matched group of healthy participants.

All participants received a single oral dose of 5 mg zibotentan under fasted conditions and were involved in the study for approximately 5 weeks.

Twelve participants were dosed in Cohort 1 and 11 participants were dosed in Cohort 2:

- Cohort 1: 12 participants with moderate hepatic impairment and moderate renal impairment as assessed at Screening.
- Cohort 2: 11 healthy participants matched for age (± 10 years), gender, and body mass index (± 20%) on a group level to participants in Cohort 1.

The study comprised of the following study periods:

- A Screening Period of maximum 28 days (before dosing): participants were screened for eligibility.
- A Residential Period of 8 days: participants were admitted to the study centre in the evening on Day -2, 2 days before administration of a single oral dose of zibotentan (Day 1). Participants had final study assessments on Day 6 (120 hours post-dose) and were discharged that day.

The study was conducted at a single centre in Bulgaria.

Target Population and Sample Size

Healthy participants and participants with moderate hepatic impairment and moderate renal impairment, male and female (of non-childbearing potential) aged 18 to 80 years (at the time of signing the informed consent), having a body mass index between 18 and 35 kg/m^2 and weighed at least 50 kg.

Twelve evaluable participants were planned to be enrolled in each group (participants with moderate hepatic and moderate renal impairment versus healthy participants).

Investigational Product: Dosage, Mode of Administration and Batch Numbers

Table S2 Study Treatment

Intervention name	Zibotentan
Type	Drug
Dose formulation	Capsule
Unit dose strength	5 mg
Dosage level	5 mg (1 capsule) single dose
Route of administration	Oral
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided by the Sponsor
Packaging and labelling	Study Intervention was provided as a bottle of 28 capsules
Special handling requirement	Drug product should be stored in the containers provided and used according to the instructions on the label and any handling instructions
Batch/Lot Number	Provided in Appendix 16.1.6 of the CSR

Abbreviations: CSR = clinical study report; IMP = investigational medicinal product;
NIMP = non-investigational medicinal product.

Duration of Treatment

All participants received a single dose of 5 mg zibotentan.

Statistical Methods

Determination of Sample Size:

CCI [redacted]

Analysis Sets:

- Screened population: All participants who sign the informed consent form.
- All dosed participant set: All participants who received the single dose of zibotentan.
- Pharmacokinetic analysis set: All participants who received the single dose of zibotentan who have at least 1 quantifiable post dose concentration and who have no important protocol deviations thought to impact on the analysis of the PK data.
- Safety analysis set: All participants who received the single dose of zibotentan and for whom any safety post-dose data are available.

Presentation and Analysis of Pharmacokinetic Data:

Pharmacokinetic blood sample collection times, including derived sampling time deviations, were listed. Plasma concentrations, urine amount excreted, and fraction of dose excreted (per collection interval and cumulative), and PK parameters were listed and presented in tabular and graphical form as appropriate. A listing of start and stop times of urine sample collection, zibotentan urine concentration, and urine volume/weight data was provided based on the all dosed participant set. Urine amount and fraction of dose excreted were listed and summarised based on the pharmacokinetic analysis set. The statistical analysis was performed using analysis of variance model, using the natural logarithm of AUClast, AUCinf, and Cmax as the response variables, and cohort as fixed effect assuming equal variance in the 2 cohorts. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for AUClast, AUCinf, and Cmax were estimated and presented by cohort. Ratios of geometric means together with CIs (2-sided 90%) were estimated and presented for

comparison between both cohorts. A regression analysis of PK parameters vs renal function was done including data from both cohorts.

Presentation and Analysis of Safety Data:

Participant disposition was listed and summarised, including number of participants screened and dosed, number and percentage of participants who completed the study, and the number and percentage of participants who were withdrawn (including reasons for withdrawal). The number of participants with screen failures and their reasons were provided. Analysis sets were summarised and include the number of participants included and excluded (displaying the reasons for exclusion) on each population set.

All safety data were presented in the data listings. Use of concomitant medication was reported. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT). Tabulations and listings of data for vital signs, electrocardiograms (ECGs; listings only), and clinical laboratory tests (including haematology and serum clinical chemistry) were presented. Urinalysis, pregnancy, follicle stimulating hormone, and body weight (together with body mass index) were listed only.

Study Population

Twenty-three participants were included in the study. Twelve participants with moderate hepatic impairment and moderate renal impairment were included in Cohort 1 and 11 healthy participants matched for age (± 10 years), gender, and BMI (± 20%) on a group level to participants in Cohort 1 were included in Cohort 2. Eleven participants in Cohort 1 completed the study as 1 participant was withdrawn from the study due to the impossibility to take repeated blood and urine samples, and numerous protocol deviations were reported. All 11 participants included in Cohort 2 completed the study.

Summary of Efficacy Results

Not applicable.

Summary of Pharmacokinetic Results

- Exposure to zibotentan was increased in renally and hepatically impaired participants in terms of AUClast and AUCinf, with geometric least squares mean (GLSM) ratios (90% CI) of 211.0% (180.6, 246.5) and 210.6% (180.3, 246.1), respectively. There was no clinically significant difference in Cmax (GLSM ratio [90% CI] of 106.8% [85.27, 133.8]), although the upper bound of the 90% CI slightly exceeded 125%.
- Differences in exposure appeared to be partly attributable to changes in renal clearance of unchanged zibotentan. Geometric mean CLR in impaired participants was 9% of matched controls, with impaired participants excreting 10% of the dose in urine compared to 55% of the dose for healthy controls. Overall CL/F in renally and hepatically impaired

participants was approximately half the value observed for matched controls and this parameter was positively correlated with estimated glomerular filtration rate (eGFR).

- Additional differences between cohorts included a slightly delayed tmax for impaired participants (median 3 hours compared to 1.5 hours post-dose for control participants), and a longer t½λz (14.7 hours versus 9.82 hours in healthy participants).

Summary of Pharmacodynamic Results

Not applicable.

Summary of Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

Summary of Pharmacogenetic Results

Not applicable.

Summary of Safety Results

- Overall, 11 (47.8%) participants, 7 (58.3%) participants in Cohort 1 and 4 (36.4%) participants in Cohort 2, experienced a total of 15 AEs during the study:
  - Cohort 1: headache reported by 6 (50.0%) participants, and single events of diarrhoea, asthenia, dizziness, circulatory collapse, and hypotension.
  - Cohort 2: headache reported by 4 (36.4%) participants.
- All events of headache, asthenia, dizziness, and hypotension reported for Cohort 1 and all events of headache reported for Cohort 2 were considered by the Investigator to be related to zibotentan. All were assessed by the Investigator to be mild in intensity, except for 3 events of headache reported by participants in Cohort 1, and 2 events of headache reported by participants in Cohort 2 that was considered by the Investigator to be moderate in intensity. All AEs resolved before the end of the study.
- No SAEs reported. No AEs that led to discontinuation of IMP or the study, or with an outcome of death were reported.
- No clinically relevant trends were observed for laboratory results and vital signs. No clinically significant abnormal ECG findings were reported, and no physical examination findings were reported as AEs.
- There were no new clinically significant safety findings for zibotentan in this study.

Conclusion

- Exposure to zibotentan was increased in renally and hepatically impaired participants in terms of AUClast and AUCinf, with GLSM ratios (90% CI) of 211.0% (180.6, 246.5) and 210.6% (180.3, 246.1), respectively. There was no clinically significant difference in Cmax (GLSM ratio [90% CI] of 106.8% [85.27, 133.8]), although the upper bound of the 90% CI slightly exceeded 125%.

- Differences in exposure appeared to be partly attributable to changes in renal clearance of unchanged zibotentan. Geometric mean CLR in impaired participants was 9% of matched controls, with impaired participants excreting 10% of dose in urine compared to 55% of dose for healthy controls. Overall CL/F in renally and hepatically impaired participants was approximately half the value observed for matched controls and this parameter was positively correlated with eGFR.
- In general, no notable difference was observed in safety profiles for impaired participants and healthy controls after administration of 5 mg zibotentan.