

Pharmacokinetics and Tolerability of Zibotentan in Patients with Concurrent Moderate Renal and Moderate Hepatic Impairment

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Supplementary Material

Supplementary Methods

Inclusion Criteria

For inclusion in the study, participants had to fulfil all of the following criteria:

Age

- Participants were between the ages of 18 and 80 years of age at the time of signing the informed consent
- The lowest age of healthy participants (Cohort 2) was not less than 10 years below the lowest age of participants with impairment (Cohort 1) and the highest age in healthy participants (Cohort 2) was not greater than 10 years above the highest age in participants with impairment (Cohort 1)

Weight

- Body weight of at least 50 kg and body mass index (BMI) within the range of 18 and 35 kg/m² (inclusive)
- BMI of healthy participants (Cohort 2) was not more than 20% below the lowest BMI of participants with impairment (Cohort 1) or more than 20% above the highest BMI of participants with impairment (Cohort 1)

Sex

- Female of non-childbearing potential or male

- There was an approximately equivalent number of male and female participants in healthy participants (Cohort 2) as in participants with impairment (Cohort 1)
- Where possible, at least 2 participants of each sex were enrolled in each of the cohorts

Reproduction and Contraception

- Male participants: all male participants used methods of contraception consistent with local regulations for those participating in clinical studies. Sterilised male participants used a barrier method of contraception (condom)
 - Non-sterilised male participants used together with their female partner/spouse a highly effective method of contraception during the entire duration of the study and for 3 months after the last dose of the study intervention
- Highly effective birth control methods were defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly, and include:
 - (i) permanent sterilisation: male vasectomy or female hysterectomy/bilateral salpingectomy/bilateral oophorectomy, combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device; and intrauterine hormone-releasing system
 - (iii) total sexual abstinence (true abstinence in line with the preferred and usual lifestyle choice of the participant)

- Female participants: Had a negative serum pregnancy test at screening and negative urine pregnancy test within 24 hours prior to dosing on Day -1, were not lactating and were of non-childbearing potential confirmed at screening. Women who were of non-childbearing potential were defined as women who were either permanently sterilised (hysterectomy, bilateral oophorectomy or bilateral salpingectomy), or who were postmenopausal. Women were considered postmenopausal if they had been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements applied:
 - (i) Women <50 years old were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range
 - (ii) Women $\geq$ 50 years old were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment
- Male participants did not donate sperm or facilitate pregnancy in any way for the duration of the study and for at least 3 months after the last safety assessment

Informed Consent

- All participants were capable of giving signed informed consent

Type of Participant and Disease Characteristics

Participants with Impairment (Cohort 1)

- An estimated glomerular filtration rate (eGFR) in the range of 30 to 45 mL/min/1.73 m² (inclusive) as determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at screening. Retesting for eGFR could have been repeated twice during the screening period
- Confirmed clinical diagnosis of cirrhosis with either ascites or moderate hepatic impairment (Child-Pugh B). Supporting documents confirming the participant's hepatic impairment were available. The participant was classified by the investigator or usual practitioner as Child-Pugh class B or having radiographic or clinical evidence of ascites of any grade
- Stable hepatic impairment (e.g., no clinically significant change in signs, symptoms or laboratory parameters of hepatic disease status within 28 days prior to screening, as determined by the investigator or usual practitioner)

Healthy Participants (Cohort 2)

- Participants who were overtly healthy as determined by medical evaluation including medical history, physical examination and clinical laboratory tests
- An eGFR of ≥ 90 mL/min/1.73 m² as determined using the CKD-EPI formula at screening
- No clinically significant liver or kidney disease as judged by the investigator

Exclusion Criteria

- Any of the following were regarded as a criterion for exclusion from the study

Medical Conditions

- Any evidence of a clinically significant disease which in the investigator's opinion made it undesirable for the participant to participate in the study
- History of alcohol abuse or excessive intake of alcohol within 6 months prior to the screening visit. Definition of excessive intake: an average weekly intake of >7 drinks/week for men or >3.5 drinks/week for women. One drink is equivalent to (16 g of alcohol)
- Positive alcohol or drug of abuse at screening
- Participants with a history of severe allergy/hypersensitivity or ongoing clinically important allergy/hypersensitivity, as judged by the investigator, to drugs with a similar chemical structure or class to zibotentan
- Participants with known hypersensitivity/allergic reaction to paracetamol
- Any of the following signs or confirmation of COVID-19 infection:
 - (i) Positive COVID-19 test result on admission to study centre on Day -2. Note:
Lateral flow testing was allowed
 - (ii) Clinical signs and symptoms consistent with COVID-19 (e.g., fever, dry cough, dyspnoea, sore throat and fatigue) 4 weeks before screening (Visit 1) or on admission to the study centre on Day -2

- (iii) Previously hospitalised with COVID-19 infection within the last 3 months

Participants with Impairment (Cohort 1)

- Presence of unstable medical (e.g., diabetes, epilepsy) or psychological conditions which, in the opinion of the investigator, would have compromised the participant's safety or successful participation in this study
- Fluctuating or rapidly deteriorating hepatic function, as indicated by strongly varying or worsening of clinical and/or laboratory signs of hepatic impairment within 28 days prior to dosing (e.g., infection of ascites, fever or active gastrointestinal bleeding)
- Severe hepatic impairment (Child-Pugh class C hepatic impairment), an isolated aspartate transaminase (AST) or alanine transaminase (ALT) >5 x the upper limit of normal (ULN); or total bilirubin >2 x ULN at time of enrolment or a concurrent increased AST and ALT of >3 x the ULN together with a total bilirubin of >2 x ULN. An isolated increase in bilirubin in participants with known Gilbert's syndrome was not a reason for exclusion
- Acute liver disease caused by drug toxicity or by an infection
- Presence of a hepatocellular carcinoma
- Liver or renal transplantation or planned within the next 3 months at screening
- Receiving renal replacement therapy

- Recent acute or subacute renal function deterioration (e.g., participants with large fluctuations of creatinine values, as judged by the investigator, and documented within 28 days prior to screening)
- New York Heart Failure Association functional heart failure Class III or IV or with unstable heart failure requiring hospitalisation for optimisation of heart failure treatment and who were not yet stable on heart failure therapy within 6 months prior to screening
- Abnormal resting vital signs (after resting for 10 minutes) of supine systolic blood pressure (BP) >180 mmHg or <100 mmHg; or diastolic BP >110 mmHg or <50 mmHg
- Change in dose regimen of medically required medication within the 14 days before dosing

Healthy Participants (Cohort 2)

- History of any clinically important disease or disorder which, in the opinion of the investigator, could have either put the participant at risk because of participation in the study, or influenced the results or the participant's ability to participate in the study

Prior/Concomitant Therapy

- Use of strong or moderate inhibitors or inducers of Cytochrome P450 3A4 within 28 days prior to dose of zibotentan
- Use of phosphate binders (e.g., aluminium hydroxide and calcium carbonate) and acid reducing agents such as cholestyramine/colestipol, ranitidine/nizatidine or proton pump inhibitors within 3 days before and 12 hours after dosing with zibotentan

Prior/Concurrent Clinical Study Experience

- Participation in another clinical study with an investigational product or device in the last 3 months
- Use of any prescribed or nonprescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, mega-dose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of study intervention or longer if the medication has a long half-life
- Participants who had previously received zibotentan within 28 days of dosing

Other Exclusions

- Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site)
- Vulnerable participants, e.g., kept in detention, protected adults under guardianship, trusteeship or committed to an institution by governmental or juridical order
- Judgement by the Investigator that the participant was not to participate in the study if the participant was unlikely to comply with study procedures, restrictions and requirements