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Absorption, Distribution, Metabolism, and Excretion of [^{14}C]-Volixibat in Healthy Men: Phase 1 Open-Label Study

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SUPPLEMENTARY MATERIAL

Appendix S1: Inclusion and Exclusion Criteria

Inclusion Criteria

Participants could not be enrolled before all inclusion criteria (including test results) were confirmed. Each participant had to meet all of the following criteria to be eligible for the study.

1. Understanding of, and ability and willingness to comply fully with, study procedures and restrictions.

2. Ability to provide voluntarily written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.

3. Aged 18–50 years, inclusive, at the time of consent. The date of signing informed consent was defined as the screening visit. This inclusion criterion was assessed only at the screening visit.

4. Male who agreed to comply with any applicable contraceptive requirements of the protocol.

5. Considered healthy. Healthy status was defined by the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead electrocardiogram (ECG), hematology, thyroid panel (included triiodothyronine [T3], thyroxine [T4], and thyroid-stimulating hormone, at screening only), blood chemistry, coagulation, and urinalysis.

6. A body mass index of 18.0–30.0 kg/m², inclusive, with a body weight >50 kg (110 lb). This inclusion criterion was assessed only at the first screening visit.

7. Ability to swallow all investigational product.

8. A minimum of one bowel movement per day.

Exclusion Criteria

Participants were excluded from the study if any of the following exclusion criteria were met.

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological, or psychiatric disease; gall bladder removal; gastric bypass surgery; ileal resection; any small intestinal resection; or current or recurrent disease that could have affected the action, absorption, or disposition of the investigational product or clinical or laboratory assessments.

2. Current or relevant history of physical or psychiatric illness, any medical disorder that may have required treatment or made the participant unlikely to complete the study fully, or any condition that presented undue risk from the investigational product or procedures.

3. Known or suspected intolerance of or hypersensitivity to the investigational product, or closely related compounds, or any of the stated ingredients.

4. Significant illness, as judged by the investigator, during the 2 weeks before administration of investigational product.

5. Known history of alcohol or other substance abuse within the last year.

6. Donation of blood or blood products (e.g., plasma or platelets) during the 60 days before administration of investigational product.

7. Within 30 days before the dose of investigational product: had used an investigational product (if the elimination half-life was <6 days; otherwise 5 half-lives); had been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may have affected this Shire-sponsored study; had had any substantial changes in eating habits, as assessed by the investigator.

8. Confirmed systolic blood pressure >139 mmHg or <89 mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.

9. Twelve-lead ECG demonstrating a corrected QT interval (QTc) >450 ms at screening. If QTc exceeded 450 ms, the ECG was to be repeated two more times and the average of the three QTc values was to be used to determine the participant's eligibility.

10. A positive screen for drugs of abuse at screening or a positive screen for alcohol or drugs of abuse at check-in (day −1).

11. Male participants who consumed more than 21 units of alcohol per week or 3 units of alcohol per day (1 alcohol unit: one beer or one glass of wine [5 oz/150 mL] or one serving of liquor [1.5 oz/40 mL] or 0.75 oz/20 mL of alcohol).

12. A positive human immunodeficiency virus antibody, hepatitis B surface antigen, or hepatitis C virus antibody screen.

13. Used tobacco in any form (e.g., smoking, chewing) or other nicotine-containing products in any form (e.g., gum, patch). Ex-users must have reported that they had stopped using tobacco for at least 30 days before receiving the dose of investigational product.

14. Routinely consumed more than two units of caffeine per day or experienced caffeine-withdrawal headaches. (One caffeine unit is contained in the following items: one 6 oz/180 mL cup of coffee; two 12 oz/360 mL cans of cola; one 12 oz/360 mL cup of tea; three 1 oz/85 g chocolate bars. Decaffeinated coffee, tea, and cola were not considered to contain caffeine.)

15. Previous screen failure or had participated or enrolled in this study.

16. Current use of any medication, including over-the-counter, herbal, or homeopathic preparations, with the exception of the occasional use of ibuprofen or acetaminophen (current use was defined as use during the 14 days before the first dose of investigational product).

17. An inability to follow a standardized diet and meal schedule or to fast, as required during the study.

18. Had participated in a [^{14}C] study within the last 6 months before the dose of investigational product. The total exposure from this and any previous study was to be within the recommended levels considered safe (e.g., <5000 mrem/year whole body annual exposure).

19. Exposure to clinically significant radiation during the 12 months before the dose of investigational product (e.g., serial X-ray or computed tomography scan, barium meal, current employment in a job requiring radiation exposure monitoring).

Appendix S2: Schedule of Assessments

Visit	Screening	Check-in	Dosing and sample collection	Sample collection	Clinic discharge[a]/early termination	Follow-up call[b]
Study day	−28 to −2	−1	1	2–6	7, 8, 9, or 10	
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demography and medical/medication history	X	X				
Body weight/height	X					
BMI	X					
Physical examination	X	X			X[c]	
12-lead ECG	X	X	X	X	X[c]	
Vital signs[d]	X	X	X	X	X[c]	
HIV, HBsAg, and HCV antibody	X					

Visit	Screening	Check-in	Dosing and sample collection	Sample collection	Clinic discharge[a]/early termination	Follow-up call[b]
Study day	−28 to −2	−1	1	2–6	7, 8, 9, or 10	
Urine drug screen	X	X				
Alcohol breath test		X				
Clinical laboratory evaluation[e]	X	X		X[f]	X[c]	
Thyroid panel	X					
In-house confinement		X	X	X	X	
Study drug administration[g]			X			
Blood pharmacokinetic/ radioanalysis samples			X	X	X[h]	
Urine collection pharmacokinetics/ radioactivity/metabolite profiling and identification			X	X	X[h]	

Visit	Screening	Check-in	Dosing and sample collection	Sample collection	Clinic discharge[a]/early termination	Follow-up call[b]
Study day	−28 to −2	−1	1	2–6	7, 8, 9, or 10	
Stool collection radioactivity/metabolite profiling and identification		X	X	X	X[h]	
Vomitus collection			X[i]			
Blood metabolite profiling and identification samples			X	X[j]	X[h]	
AE evaluations	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X

AE adverse event, *BMI* body mass index, *ECG* electrocardiogram, *HBsAg* hepatitis B surface antigen, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *SAE* serious adverse event

[a]Participants were discharged from the clinical research center on day 7 (6 days after dosing) if they met the discharge criteria. Any participants who did not meet the discharge criteria on day 7 could remain in the unit up to day 10, when they were discharged regardless of radioactivity measurements

[b]There was a follow-up telephone call approximately 7 ± 2 days following clinic discharge to follow up on safety assessments including any ongoing AEs/SAEs and changes in concomitant medications. AEs/SAEs occurring up to the time of the follow-up telephone call were captured. The follow-up telephone call was to be made for all participants, including those who withdrew or were removed from the study before day 7

[c]Participants who withdrew early underwent discharge assessments

[d]Vital signs (blood pressure and pulse rate measured after the participant had been supine for at least 5 minutes) were recorded at all time points. Oral temperature and respiratory rate were measured at screening, day −1, and clinic discharge

[e]Clinical laboratory evaluations included serum biochemistry, hematology, coagulation, and urinalysis

[f]Clinical laboratory evaluations were performed on day 3

[g]Participants received a single oral dose of [^{14}C]-volixibat 50 mg containing approximately 5.95 μCi radioactivity before breakfast on the morning of day 1

[h]Pharmacokinetic and metabolite profiling and identification samples were collected on day 7

[i]Vomitus collected within 4 hours after dosing (as applicable) was stored frozen for possible radioanalysis

[j]Samples for plasma metabolite profiling were collected on day 2

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Appendix S3: Detailed Time and Events Schedule

Study day	Time in relation to dosing (hours)	Study drug administration	Vital signs	12-lead ECG	Clinical laboratory evaluation	Blood PK samples[a]	Blood radioanalysis samples	Plasma metabolite samples[b]	Urine collection intervals[c]	Stool collection intervals[d]
Day 1	Pre-dose		X[e]	X[e]		X[e]	X[e]	X[e]	X[f]	X[f]
	0	X							X[g]	X[h]
	0.5					X	X		↓	↓
	1					X	X		↓	↓
	1.5		X	X		X	X		↓	↓
	2					X	X	X	↓	↓
	3		X	X		X	X		↓	↓
	4					X	X	X	X[g]	↓
	6		X	X		X	X		↓	↓
	8					X	X	X	X[g]	↓
	12					X	X		X[g]	↓

Study day	Time in relation to dosing (hours)	Study drug administration	Vital signs	12-lead ECG	Clinical laboratory evaluation	Blood PK samples[a]	Blood radioanalysis samples	Plasma metabolite samples[b]	Urine collection intervals[c]	Stool collection intervals[d]
Day 2	24		X	X		X	X	X	X[g]	X[h]
	36					X	X		X[g]	↓
Day 3	48		X	X	X	X	X		X[g]	X[h]
Day 4	72		X	X		X	X		X[g]	X[h]
Day 5	96		X	X		X	X		X[g]	X[h]
Day 6	120		X	X		X	X		X[g]	X[h]
Day 7	144		X	X	X	X	X	X	X[g]	X[h]

ECG electrocardiogram, *PK* pharmacokinetic

[a]For evaluation of volixibat concentrations in plasma

[b]For evaluation of radioactivity concentrations in plasma and whole blood. If discharge criteria were not met by day 7, and the radioactivity in the blood and plasma remained measurable, then blood and plasma radioanalysis samples continued to be collected on a daily basis (i.e., at 168, 192, and 216 hours) until discharge criteria were met or until day 10

[c]Urine was collected for PK analysis, radioanalysis, and metabolite profiling and identification

[d]Stool was collected for PK analysis, radioanalysis, and metabolite profiling and identification

[e]Pre-dose evaluations were to occur during the 45 minutes before dosing

[f]Pre-dose PK and radioanalysis urine samples were single void samples collected in the morning before dosing. Pre-dose radioanalysis fecal samples were single void samples collected in the 24 hours before dosing

[g]Urine PK and radioanalysis collection intervals were 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–72, 72–96, 96–120, and 120–144 hours

[h]Stool radioanalysis collection intervals were 0–24, 24–48, 48–72, 72–96, 96–120, and 120–144 hours