Poster 430

Comparative Bioavailability of Sebetralstat Following Administration of Orally Disintegrating Tablets and Film-Coated Tablets in Healthy Volunteers

Michael D. Smith,[1] Matthew Iverson,[1] Erik Hansen,[1] Paul K. Audhya,[1] Christopher M. Yea[1]

[1]KalVista Pharmaceuticals, Cambridge, MA, USA; KalVista Pharmaceuticals, Salisbury, United Kingdom

Background

- Hereditary angioedema (HAE) is a genetic disorder manifesting as unpredictable attacks of tissue swelling caused by uncontrolled activation of the kallikrein-kinin system[1]
- Currently, all approved on-demand treatments for HAE attacks must be administered parenterally[2]
- People with HAE reported a desire to use oral therapies rather than parenteral therapies[3]
- Sebetralstat is a novel oral plasma kallikrein inhibitor that is currently being investigated in a phase 3 trial as an on-demand treatment for HAE attacks[4]
- An orally disintegrating tablet (ODT) formulation of sebetralstat is being developed to provide people with HAE more options to help them manage their disease

Objectives

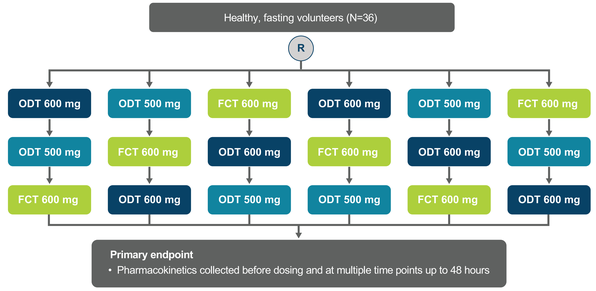
- To compare the single-dose pharmacokinetics of sebetralstat following administration of ODTs or film-coated tablets (FCTs) in healthy adult participants
- To determine the safety and tolerability of a single dose of sebetralstat ODT in healthy adult participants

Methods

Study Design

- This was an open-label, randomized, comparative bioavailability crossover trial (**Figure 1**)
- Healthy volunteers were administered sebetralstat as a single dose of 600 mg FCT (2 × 300 mg), 600 mg ODT (2 × 300 mg), or 500 mg ODT (2 × 250 mg) under fasting conditions
- A washout period of at least 4 days was included between doses

Figure 1. Model Diagram



FCT, film-coated tablets; ODT, orally disintegrating tablets; R, randomization.

Endpoints

- Plasma concentrations of sebetralstat were determined using a validated liquid chromatography-mass spectrometry method
- Concentration-time curves were assessed for the following parameters:
  - Area under the concentration-time curve from time 0 to the last observed nonzero concentration ($AUC_{0\text{-}t}$) or extrapolated to infinity ($AUC_{0\text{-}inf}$)
  - Maximum observed plasma concentration (C_{max})
  - Time to maximum observed plasma concentration (t_{max})
- Safety was evaluated through collection of treatment-emergent adverse events (AEs)

Statistics

- Relative bioavailabilities of the ODT formulations (test) and FCT formulation (reference) of sebetralstat were assessed by performing an analysis of variance (ANOVA) model using SAS® PROC MIXED, with sequence, treatment, and period as fixed effects and participant nested within each sequence as a random effect (mixed effects model)

Results

Participants

- 36 healthy volunteers (69% female, 31% male) were recruited to the study
- Participants self-reported race as White (83%), Black (11%), or mixed race (6%). Ethnicities were self-reported as Hispanic or Latino (83%) or not Hispanic or Latino (17%)
- The mean age was 36.1 ± 9.92 years, and the mean body mass index was 26.84 ± 3.56 kg/m²

Pharmacokinetics

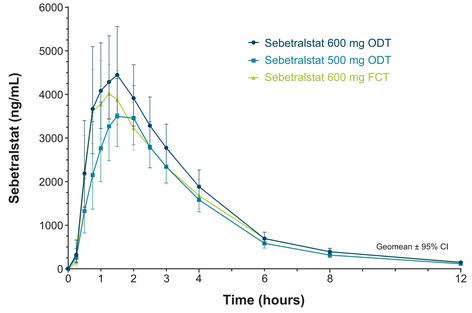
- Mean plasma concentrations for sebetralstat 500 mg ODT, 600 mg ODT, and 600 mg FCT are shown in **Figure 2**
- Plasma sebetralstat exposure was slightly higher for 600 mg ODT and slightly lower for 500 mg ODT compared with 600 mg FCT (**Table 1**)
- The median t_{max} values were the same following 600 mg ODT and 600 mg FCT and increased slightly for 500 mg ODT compared with 600 mg FCT
- The geometric least squares mean (LSM) $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ values were slightly lower for sebetralstat 500 mg ODT (**Table 2**) and slightly higher for sebetralstat 600 mg ODT (**Table 3**) compared with 600 mg FCT, with the 90% CIs of the geometric mean ratio (GMR) for both dosages entirely within the 80.00%-125.00% bioequivalence limit
- Geometric LSM C_{max} value was comparable following sebetralstat 500 mg ODT and approximately 21% higher following sebetralstat 600 mg ODT compared with 600 mg FCT

Table 1. Plasma Sebetralstat Pharmacokinetic Parameters Following Administration of a Single Oral Dose

	600 mg ODT		500 mg ODT		600 mg FCT	
	n	Value	n	Value	n	Value
$AUC_{0\text{-}t}$, geometric mean (CV%), ng·h/mL	36	19,600 (40.4)	36	15,800 (37.9)	36	17,900 (38.5)
$AUC_{0\text{-}inf}$, geometric mean (CV%), ng·h/mL	35	20,500 (33.2)	36	16,000 (37.4)	35	18,300 (37.6)
C_{max}, geometric mean (CV%), ng/mL	36	6120 (54.2)	36	5070 (48.6)	36	5040 (51.5)
t_{max}, median (minimum, maximum), h	36	0.99 (0.50, 4.1)	36	1.3 (0.50, 4.0)	36	0.99 (0.50, 3.0)

$AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}inf}$, area under the concentration-time curve for time 0 to the last observed nonzero concentration; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; FCT, film-coated tablet; ODT, orally disintegrating tablet; t_{max}, time to reach maximum observed plasma concentration.

Figure 2. Geometric Mean Plasma Concentrations After a Single Dose of Sebetralstat ODT or FCT



Geomean, geometric mean; FCT, film-coated tablet; ODT, orally disintegrating tablet.

Table 2. Summary of Statistical Comparisons of Plasma Sebetralstat Pharmacokinetic Parameters Following Administration of a Single Dose of 500 mg ODT Versus 600 mg FCT

	500 mg ODT (Test)		600 mg FCT (Reference)				
	n	Geometric LSMs	n	Geometric LSMs	GMR (%)	90% CI	Intra-Participant CV%
$AUC_{0\text{-}t}$, ng·h/mL	36	15,800	36	17,900	88.34	81.84-95.35	19.63
$AUC_{0\text{-}inf}$, ng·h/mL	36	16,000	35	18,300	87.44	81.35-93.99	18.32
C_{max}, ng/mL	36	5070	36	5040	100.48	89.56-112.72	29.90

ANOVA, analysis of variance; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve for time 0 to the last observed nonzero concentration; C_{max}, maximum observed concentration; CV%, coefficient of variation; FCT, film-coated tablet; GMR, geometric mean ratio; LSM, least squares mean; ODT, orally disintegrating tablet.

ANOVA model using SAS® PROC MIXED was used. The ANOVA included sequence, treatment, and period as fixed effects and participant within sequence as a random effect.

The terminal elimination rate was not calculable for one patient after the 600 mg FCT treatment.

Table 3. Summary of Statistical Comparisons of Plasma Sebetralstat Pharmacokinetic Parameters Following Administration of a Single Dose of 600 mg ODT Versus 600 mg FCT

	600 mg ODT (Test)		600 mg FCT (Reference)				
	n	Geometric LSMs	n	Geometric LSMs	GMR (%)	90% CI	Intra-Participant CV%
$AUC_{0\text{-}t}$, ng·h/mL	36	19,600	36	17,900	109.33	101.28-118.01	19.63
$AUC_{0\text{-}inf}$, ng·h/mL	35	20,200	35	18,300	110.83	103.03-119.22	18.32
C_{max}, ng/mL	36	6120	36	5040	121.35	108.16-136.14	29.90

ANOVA, analysis of variance; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve for time 0 to the last observed nonzero concentration; C_{max}, maximum observed concentration; CV%, coefficient of variation; FCT, film-coated tablet; GMR, geometric mean ratio; LSM, least squares mean; ODT, orally disintegrating tablet.

ANOVA model using SAS® PROC MIXED was used. The ANOVA included sequence, treatment, and period as fixed effects and participant within sequence as a random effect. Parameters were ln-transformed prior to analysis.

The terminal elimination rate was not calculable for one patient after the 600 mg ODT treatment and one patient after the 600 mg FCT treatment.

Geometric LSMs are calculated by exponentiating the LSMs derived from the ANOVA.

GMR was calculated as 100 × (test/reference).

Intra-participant CV% was calculated as 100 × square root ($\exp\{MSE\}-1$), where mean squared error (MSE) represents residual variance from ANOVA.

Safety

Table 4. Safety

	600 mg ODT N=36	500 mg ODT N=36	600 mg FCT N=36
Number of participants with treatment-emergent AEs, n (%)	5 (14)	3 (8)	7 (19)
Gastrointestinal disorders	**3 (8)**	**2 (6)**	**4 (11)**
Abdominal discomfort	0 (0)	0 (0)	1 (3)
Abdominal pain	1 (3)	0 (0)	0 (0)
Abdominal pain lower	0 (0)	0 (0)	1 (3)
Constipation	1 (3)	1 (3)	2 (6)
Dyspepsia	0 (0)	0 (0)	1 (3)
Flatulence	0 (0)	0 (0)	1 (3)
Hypoesthesia oral	0 (0)	1 (3)	0 (0)
Nausea	1 (3)	0 (0)	0 (0)
Rectal hemorrhage	0 (0)	0 (0)	1 (3)
General disorders and administrative site conditions	**1 (3)**	**0 (0)**	**0 (0)**
Vessel puncture site pain	1 (3)	0 (0)	0 (0)
Infections and infestations	**1 (3)**	**0 (0)**	**1 (3)**
Asymptomatic bacteriuria	0 (0)	0 (0)	1 (3)
Pharyngitis	1 (3)	0 (0)	0 (0)
Injury, poisoning, and procedural complications	**0 (0)**	**0 (0)**	**1 (3)**
Limb injury	0 (0)	0 (0)	1 (3)
Musculoskeletal and connective tissue disorders	**0 (0)**	**1 (3)**	**0 (0)**
Back pain	0 (0)	1 (3)	0 (0)
Nervous system disorders	**2 (6)**	**0 (0)**	**1 (3)**
Dizziness	2 (6)	0 (0)	0 (0)
Headaches	1 (3)	0 (0)	0 (0)
Somnolence	0 (0)	0 (0)	1 (3)
Psychiatric disorders	**0 (0)**	**1 (3)**	**0 (0)**
Euphoric mood	0 (0)	1 (3)	0 (0)
Renal and urinary disorders	**0 (0)**	**0 (0)**	**1 (3)**
Urinary retention	0 (0)	0 (0)	1 (3)

AE, adverse event; FCT, film-coated tablet; ODT, orally disintegrating tablet.

- No deaths, serious AEs, or discontinuation due to AEs occurred during the trial
- The most frequently reported AE was constipation, which was experienced by 4 participants (11%) treated with sebetralstat ODT or FCT (**Table 4**)

Conclusions

- **Plasma exposure was slightly lower for 500 mg ODT and slightly higher for 600 mg ODT compared with 600 mg FCT**
  - **Geometric LSM AUC values were slightly lower for 500 mg ODT and slightly higher for 600 mg ODT compared with 600 mg FCT with 90% CIs for both dosages within the 80.00-125.00% bioequivalence range**
- **Single doses of 500 mg or 600 mg sebetralstat administered in ODT or FCT were well tolerated in healthy adult participants enrolled in this trial**
- **These data support further clinical development of an ODT formulation for people living with HAE**

References

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