Supplementary Material

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Positive Modulator of HGF/MET, Fosgonimeton, in Healthy Volunteers and Subjects with Alzheimer's Disease: Randomized, Placebo-Controlled, Double-Blind, Phase I Clinical Trial

Supplementary Table 1. Summary of TEAEs in single ascending dose study of fosgonimeton in healthy young subjects (part A)

	Placebo	**Fosgonimeton**					
TEAE, n (%)	**n = 12**	**2 mg n = 6**	**6 mg n = 6**	**20 mg n = 6**	**40 mg n = 6**	**60 mg n = 6**	**90 mg n = 6**
All	2 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	0 (0)	2 (33.3)	1 (16.7)
Abdominal pain	1 (8.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[b]	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[b]	0 (0)
Dyspepsia	0 (0)	0 (0)	1 (16.7)[b]	0 (0)	0 (0)	0 (0)	0 (0)
Flatulence	1 (8.3)[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Catheter site pain	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[a]	0 (0)
Injection site pruritus	0 (0)	0 (0)	0 (0)	1 (16.7)[a]	0 (0)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[b]
Headache	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)
Psychogenic seizure	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[c]	0 (0)
Pruritus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)[b]	0 (0)
Pseudofolliculitis barbae	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)

[a]Related to treatment. [b]Possibly related to treatment. [c]Unlikely to be related to treatment.
TEAE, treatment-emergent adverse event.

Supplementary Table 2. Summary of TEAEs in multiple ascending dose study of fosgonimeton in healthy elderly subjects (part B)

	Placebo	**Fosgonimeton**			
TEAE, n (%)	**n = 7**	**20 mg n = 6**	**40 mg n = 6**	**60 mg n = 6**	**80 mg n = 4**
All	3 (42.9)	1 (16.7)	4 (66.7)	2 (33.3)	3 (75.0)
Neutropenia	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)
Constipation	1 (14.3)[c]	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	1 (14.3)[c]	1 (16.7)[c]	1 (16.7)[c]	1 (16.7)[c]	2 (50.0)[d]
Dry mouth	0 (0)	0 (0)	0 (0)	1 (16.7)[c]	0 (0)
Dyspepsia	0 (0)	0 (0)	1 (16.7)[c]	0 (0)	0 (0)
Flatulence	0 (0)	0 (0)	1 (16.7)[c]	0 (0)	0 (0)
Nausea	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)
Asthenia	0 (0)	0 (0)	1 (16.7)[c]	0 (0)	0 (0)
Chest pain	0 (0)	1 (16.7)	1 (16.7)	0 (0)	0 (0)
Injection site pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)[a]
Injection site pruritus	0 (0)	0 (0)	1 (16.7)[a]	0 (0)	0 (0)
Hypersensitivity	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)[b]
Fall	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)
Pain in extremity	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)
Dizziness	0 (0)	0 (0)	2 (33.3)[c]	1 (16.7)[c]	1 (25.0)[c]
Headache	0 (0)	1 (16.7)[c]	1 (16.7)[c]	2 (33.3)[e]	1 (25.0)[c]
Upper-airway cough syndrome	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)

[a]Related to treatment. [b]Probably related to treatment. [c]Possibly related to treatment. [d]1 Diarrhea event probably related to treatment; 1 unlikely.
[e]2 Subjects experienced n = 3 headache events; 2 out of 3 headache events were classified as possibly related to treatment, 1 out of 3 as unrelated.
TEAE, treatment-emergent adverse event.

Supplementary Table 3. Summary of TEAEs in fixed-dose, multiple-dose study of fosgonimeton in AD subjects

TEAE, n (%)	**Placebo, n = 4**	**Fosgonimeton 40 mg, n = 7**
All	2 (50.0)	5 (71.4)
Constipation	0 (0)	1 (14.3)[a]
Feces soft	0 (0)	1 (14.3)[a]
Nausea	0 (0)	1 (14.3)[a]
Catheter site hematoma	0 (0)	1 (14.3)
Injection site erythema	1 (25.0)[a]	3 (42.9)[a]
Injection site hematoma	2 (50.0)	1 (14.3)
Medical device site erythema	0 (0)	1 (14.3)
Pain in extremity	1 (25.0)[a]	0 (0)
Dizziness postural	1 (25.0)	0 (0)
Cough	0 (0)	1 (4.3)

[a]Possibly related to treatment.
AD, Alzheimer's disease; TEAE, treatment-emergent adverse event.

Supplementary Table 4. Pharmacokinetic parameters of the active metabolite ATH-1001 following a single dose or multiple doses of fosgonimeton

			Parameter[a]				
Population	**Fosgonimeton Dose**	**Day**	**C_{max} (ng/mL)**	**t_{max} (h)**	**$AUC_{0\text{-}inf}$ (ng•h/mL)**	**$t_{1/2}$ (h)[d]**	**R_{ss}**
Healthy young adult subjects (n = 35)[b]	2 mg	1	14.1 (41)	0.38 (0.08–0.5)	19.5 (38)	0.74 (22)	NA
	6 mg	1	41.7 (13)	0.50 (0.25–0.5)	65.9 (18)	1.0 (35)	NA
	20 mg	1	161 (34)	0.50 (0.25–1.0)	266 (15)	1.2 (25)	NA
	40 mg	1	245 (22)	0.50 (0.17–1.0)	414 (16)	1.8 (63)	NA
	60 mg	1	396 (21)	0.50 (0.5–0.5)	692 (16)	1.3 (19)	NA
	90 mg	1	581 (21)	0.50 (0.5–1.0)	1082 (15)	1.9 (67)	NA
Healthy elderly subjects (n = 22)[c]	20 mg	1	142 (34)	1.0 (0.5–1.0)	278 (17)	1.3 (3.6)	0.95 (6)
		9	153 (28)	0.75 (0.5–1.0)	265 (17)	1.7 (80)	
	40 mg	1	300 (32)	0.50 (0.5–1.0)	547 (17)	1.5 (12)	0.92 (8)
		9	332 (24)	0.50 (0.25–0.5)	525 (13)	4.5 (72)	
	60 mg	1	500 (22)	1.0 (0.5–1.0)	1004 (15)	1.7 (21)	0.99 (9)
		9	525 (29)	1.0 (0.5–1.0)	1008 (16)	5.0 (23)	
	80 mg	1	563 (40)	1.0 (0.5–1.0)	1082 (24)	1.5 (25)	0.94 (7)
		9	489 (43)	0.5 (0.5–1.5)	959 (27)	5.4 (47)	
AD subjects (n = 7)	40 mg	1	360 (28)	0.50 (0.25–1.0)	618 (19)	1.6 (27)	1.0 (10)
		9	352 (24)	0.50 (0.5–1.5)	640 (20)	3.0 (87)	

[a]Each parameter is summarized as geometric mean (%CV_b) except for t_{max}, which is presented as median (range). [b]Each dose level had n = 6 subjects except for the 60 mg group, which had n = 5 subjects. [c]Each dose level had n = 6 subjects each except for the 80 mg group, which had n = 4 subjects. [d]A terminal elimination phase with longer half-life was present at higher doses and is related to concentration values being detected near the limit of detection. Overall, the working half-life responsible for clearance of most of the drug is ~1.5 h. AD, Alzheimer's disease; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum observed plasma concentration; CV_b coefficient of variation between subjects; h, hour; NA, not applicable; R_{ss}, accumulation ratio at steady state; T_{max}, time to reach maximum observed plasma concentration.

Supplementary Table 5. Pharmacokinetic parameters of fosgonimeton following a single dose or multiple doses of fosgonimeton

			Parameter[a]				
Population	**Fosgonimeton Dose**	**Day**	**C_{max} (ng/mL)**	**t_{max} (h)**	**$AUC_{0\text{-}inf}$ (ng•h/mL)**	**$t_{1/2}$ (h)**	**R_{ss}**
Healthy young adult subjects (n = 35)[b]	2 mg	1	5.04 (117)	0.21 (0.08–0.5)	2.77 (90)	0.31 (32)	NA
	6 mg	1	18.8 (35)	0.21 (0.08–0.5)	15.6 (31)	0.27 (20)	NA
	20 mg	1	69.8 (28)	0.25 (0.08–0.5)	57.7 (24)	0.31 (38)	NA
	40 mg	1	147 (86)	0.21 (0.17–0.5)	113 (35)	0.33 (26)	NA
	60 mg	1	139 (76)	0.50 (0.17–0.5)	132 (62)	0.33 (7)	NA
	90 mg	1	204 (66)	0.25 (0.17–0.5)	189 (38)	0.32 (8)	NA
Healthy elderly subjects (n = 22)[c]	20 mg	1	55.2 (62)	0.38 (0.08–1.0)	62.36 (31)	0.34 (33)	0.65 (64)
		9	41.8 (101)	0.38 (0.08–0.5)	37.3 (86)	0.27 (26)	
	40 mg	1	129 (39)	0.5 (0.17–0.5)	118 (24)	0.30 (19)	0.70 (41)
		9	142 (23)	0.17 (0.17–0.5)	89.0 (49)	0.22 (11)	
	60 mg	1	139 (47)	0.38 (0.17–0.5)	142 (23)	0.27 (37)	1.2 (29)
		9	158 (35)	0.25 (0.17–0.5)	165 (28)	0.23 (19)	
	80 mg	1	261 (71)	0.38 (0.25–0.5)	252 (34)	0.27 (17)	0.88 (45)
		9	259 (80)	0.25 (0.17–0.25)	149.5 (4)	0.22 (19)	
AD subjects (n = 7)	40 mg	1	159 (43)	0.25 (0.17–0.5)	134 (43)	0.25 (16)	1.1 (35)
		9	169 (40)	0.35 (0.17–1.5)	150 (34)	0.26 (16)	

[a]Each parameter is summarized as geometric mean (%CV_b) except for T_{max}, which is presented as median (range). [b]Each dose level had n = 6 subjects except for the 60 mg group, which had n = 5 subjects. [c]Each dose level had n = 6 subjects each except for the 80 mg group, which had n = 4 subjects. AD, Alzheimer's disease; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity; C_{max}, maximum observed plasma concentration; CV_b coefficient of variation between subjects; h, hour; NA, not applicable; R_{ss}, accumulation ratio at steady state; T_{max}, time to reach maximum observed plasma concentration.

Supplementary Figure 1. Pharmacokinetic profile of fosgonimeton after single and multiple once-daily SC doses. A) Plasma concentration of fosgonimeton in healthy young volunteers after single SC dose of 2–90 mg (arithmetic mean ± SD). B) Plasma $AUC_{0\text{-inf}}$ of fosgonimeton in healthy young volunteers after a single SC dose demonstrated dose linearity ($R^2 = 0.977$, arithmetic mean ± SD). C) Plasma concentrations of fosgonimeton in healthy elderly volunteers on Day 1 (black circle) and Day 9 (open square) after once-daily SC injections of 60 mg showed no appreciable accumulation and similar exposures between Day 1 and Day 9 (arithmetic mean ± SD). AUC, area under the plasma concentration-time curve from time zero to infinity; SC, subcutaneous; SD, standard deviation.