P1050

Results From SHAPE: A Phase 2 Trial of Fosgonimeton in Patients with Parkinson's Disease Dementia or Dementia with Lewy Bodies

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CONCLUSIONS

1. In SHAPE, a small exploratory trial, fosgonimeton had a favorable safety and tolerability profile in participants with PDD or DLB; in the fosgonimeton 40 mg arm, ADAS-Cog13 changes were suggestive of a procognitive effect, shown for the first time in PDD or DLB
2. Safety and efficacy outcomes of SHAPE support continued development of fosgonimeton at the 40 mg dose level
3. The ongoing phase 2/3 LIFT-AD trial of fosgonimeton in participants with AD will provide additional insight into the ability of fosgonimeton to affect cognition

KEY TAKEAWAY

Together with results from preclinical studies and other clinical trials, the observations presented here suggest that positive modulation of the neurotrophic HGF system may be a potential therapeutic approach for people with neurodegenerative diseases, including PDD, DLB, and AD

INTRODUCTION

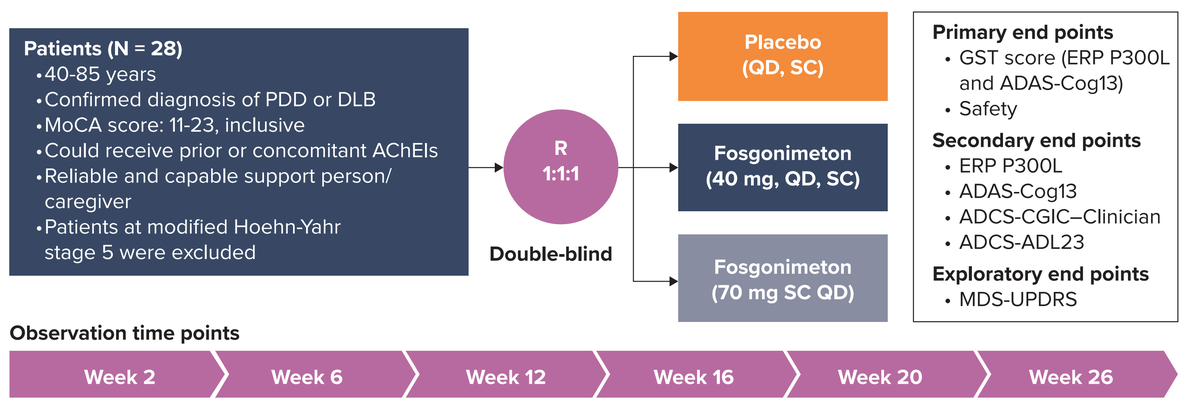
- Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are neurodegenerative, progressive diseases that result in overt changes in cognition and function[1-4]
  - These clinical changes are driven by complex pathology, including protein aggregations, leading to dysfunction in synapses and neuronal death
- Positive modulation of the neurotrophic HGF system with fosgonimeton has shown neuroprotective and procognitive effects in preclinical studies[5-7]
  - See posters P0256 and P1046 here at AD/PD 2024 for the latest preclinical data with fosgonimeton
- Because its proposed mechanism engages intrinsic maintenance and repair pathways, fosgonimeton has the potential to address a broad range of neurodegenerative diseases, including PDD, DLB, and AD
- Here, we report findings from the exploratory phase 2, multicenter, randomized, double-blind, placebo-controlled SHAPE trial, which evaluated fosgonimeton in participants with PDD or DLB

OBJECTIVE

To explore the safety and clinical effects of fosgonimeton in participants with PDD or DLB

METHODS

Figure 1. SHAPE was a randomized, double-blind, 26-week trial in participants with PDD or DLB



- SHAPE was originally designed to enroll 75 participants, but screening was electively ended in November 2022 due to design limitations and prioritization of resources

RESULTS

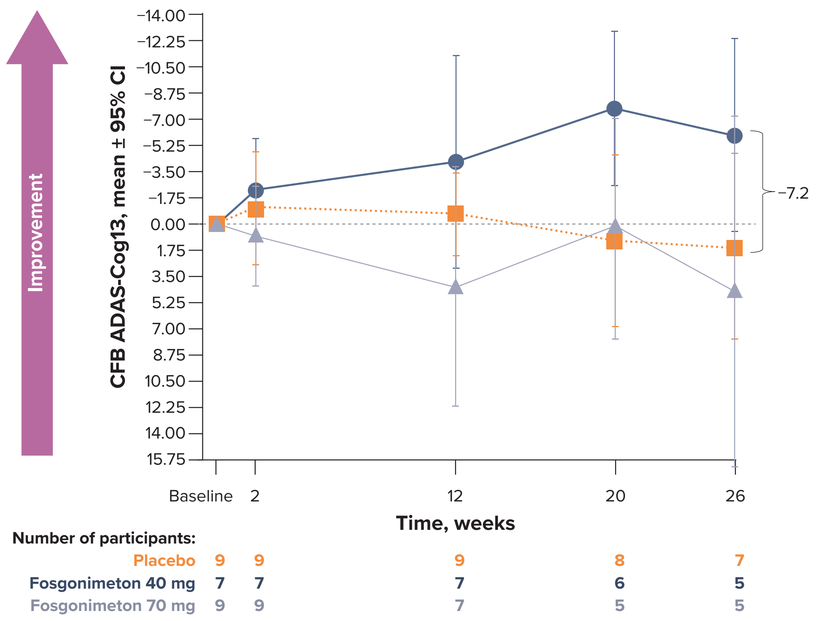
Table 1. Demographics and baseline characteristics are heterogeneous across treatment arms

Demographic or baseline characteristic	Placebo (n = 9)	Fosgonimeton 40 mg (n = 9)	Fosgonimeton 70 mg (n = 10)
Age, median (min-max), years	75 (67-81)	69 (54-83)	75 (57-82)
Ethnicity, n (%)			
Hispanic or Latino	0	0	1 (10.0)
Not Hispanic or Latino	9 (100.0)	9 (100.0)	9 (90.0)
Race, n (%)			
White	8 (88.9)	9 (100.0)	10 (100.0)
Other	1 (11.1)	0	0
Sex, n (%)			
Male	5 (55.6)	8 (88.9)	8 (80.0)
Female	4 (44.4)	1 (11.1)	2 (20.0)
Disease type, n (%)			
PDD	6 (66.7)	5 (55.6)	9 (90.0)
DLB	3 (33.3)	4 (44.4)	1 (10.0)
AChEIs, n (%)			
Yes	1 (11.1)	3 (33.3)	3 (30.0)
Baseline measurements			
MMSE, median (min-max)	26.0 (20-30)	21.0 (15-27)	26.0 (17-30)
MoCA score, median (min-max)	20.0 (16-22)	17.0 (13-23)	18.5 (11-23)
ADAS-Cog13 score, median (min-max)[a]	14.0 (9-26)	33.0 (18-43)	22.0 (7-41)
ERP P300L, median (min-max), ms[a]	391.60 (297.9-472.7)	371.09 (343.8-396.5)	374.02 (293.9-417.0)
GST score (ADAS-Cog13 and ERP P300L), median (min-max)[a]	−0.158 (−1.53-0.46)	0.336 (−0.62-1.25)	0.152 (−1.64-1.21)

[a]Modified intention-to-treat population consisted of all randomly assigned participants who received at least one dose of the study drug and who completed both an ADAS-Cog13 and an ERP P300L assessment during baseline and had at least one post-baseline visit: placebo, n = 9; fosgonimeton 40 mg, n = 7; fosgonimeton 70 mg, n = 9.

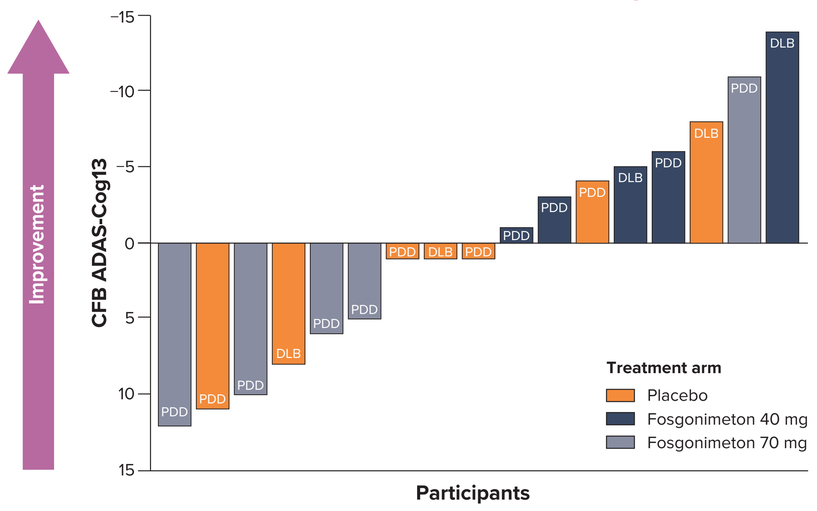
- For the 28 participants who were randomly assigned before the end of recruitment, the primary end point of CFB at 26 weeks in GST composite scores (combining ERP P300L and ADAS-Cog13 results) was not met
  - CFB in GST score in the fosgonimeton arms was not significantly different from that in the placebo arm (mean ± SD; fosgonimeton 40 mg [n = 7], −0.524 ± 0.741; fosgonimeton 70 mg [n = 9], 0.534 ± 0.942; placebo [n = 9], −0.007 ± 0.626)

Figure 2. Participants treated with fosgonimeton 40 mg show directional improvement in ADAS-Cog13 through 26 weeks



Note that ADAS-Cog13 scores were imbalanced between treatment groups at baseline.
Data presented as CFB mean ± SEM; one-sided test vs placebo ($p = 0.032$).

Figure 3. Participants in the fosgonimeton 40 mg arm at 26 weeks show directional improvements in ADAS-Cog13



- All participants treated with fosgonimeton 40 mg showed directional improvement at week 26

Table 2. Fosgonimeton shows a favorable safety profile

	Placebo (n = 9)	Fosgonimeton 40 mg (n = 9)	Fosgonimeton 70 mg (n = 10)
Duration of exposure, median (range), days	182 (112-203)	181 (64-183)	138 (4-188)
Participants with ≥1 TEAE, n (%)	7 (77.8)	9 (100.0)	9 (90.0)
Participants with ≥1 treatment-related TEAE, n (%)	2 (22.2)	8 (88.9)	7 (70.0)
Participants with serious or other significant TEAEs, n (%)	1 (11.1)	1 (11.1)	1 (10.0)
Death, n (%)	0	0	1 (10.0)
TEAEs leading to study drug withdrawal, n (%)	1 (11.1)	0	4 (40.0)
TEAEs leading to study drug interruption, n (%)	1 (11.1)	2 (22.2)	0

- The most common TEAE observed in the fosgonimeton treatment arms was injection site reaction
- No substantial differences in TEAE rates were observed between treatment arms

Abbreviations **AChEIs**, acetylcholinesterase inhibitors; **AD**, Alzheimer's disease; **ADAS-Cog13**, Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; **ADCS-ADL23**, Alzheimer's Disease Cooperative Study-Activities of Daily Living, 23-item version; **ADCS-CGIC**, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; **CFB**, change from baseline; **DLB**, dementia with Lewy bodies; **ERP P300L**, event-related potential P300 latency; **GST**, global statistical test; **HGF**, hepatocyte growth factor; **MMSE**, Mini-Mental State Examination; **MoCA**, Montreal Cognitive Assessment; **MDS-UPDRS**, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; **PDD**, Parkinson's disease dementia; **QD**, once daily; **R**, randomly assigned; **SC**, subcutaneous; **SD**, standard deviation; **SEM**, standard error of the mean; **TEAE**, treatment-emergent adverse event.

References **1.** Calabresi P et al. *Cell Death Dis*. 2023;14:176. **2.** Galasko D. *Neurol Clin*. 2017;35:325-338. **3.** Jellinger KA, Korczyn AD. *BMC Med.* 2018;16:34. **4.** Menšíková K et al. *NPJ Parkinsons Dis*. 2022;8:3. **5.** Johnston JL et al. *Neurotherapeutics*. 2023;20:431-451. **6.** Reda S et al. Presented at: 75th American Academy of Neurology (AAN) Annual Meeting; April 22-27, 2023; Boston, MA. **7.** Setti SE et al. Presented at: Neuroscience Annual Meeting; November 11-15, 2023; Washington, DC. NANO76.02.

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Disclosures

KJC, K-BCO, MDH, SES, and HJM are employees of Athira Pharma, Inc. (Athira), which is developing positive modulators of neurotrophic HGF for the potential treatment of various neurodegenerative disorders. These authors additionally hold shares of stock and/or stock options in Athira. DB receives funding and study material support from Athira; receives funding support from Praxis Precision Medicine, Jazz Pharmaceuticals, Neuraly, AbbVie Inc, Impac, Pharma 2B, Cerevel Therapeutics, Intec Pharma, Biogen, Merck, and Sage Therapeutics; and participates on the advisory board for Praxis Precision Medicine.

Disclaimer

Fosgonimeton is an investigational therapy that has not received FDA approval nor has it been demonstrated safe or effective for any use.

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