ALZHEIMER'S ASSOCIATION AAIC 22

The PIONEER Study: A Multi-center, Randomized, Double-blind, Placebo-controlled Phase 2 Trial of the Effects of T3D-959 on Safety, Cognition, Function and Plasma Biomarkers in Mild to Moderate Alzheimer's Disease Subjects: Study Update

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INTRODUCTION

T3D-959 is a novel (non-amyloid/non-tau-directed) new chemical entity aimed at improving dysfunctional brain glucose energy and lipid metabolism in Alzheimer's disease (AD)[1-4]. Dysfunctional brain metabolism in AD results from increasing resistance to insulin. Insulin resistance contributes to amyloid plaque formation, tau tangle formation and inflammation. T3D-959, a brain-penetrant, small molecule dual nuclear receptor agonist, acts as an insulin sensitizer to overcome insulin resistance to restore and maintain metabolic homeostasis. The primary target of T3D-959 is PPAR delta and secondary target is PPAR gamma. PPAR delta is ubiquitously expressed in the brain. The objectives of the Phase 2 PIONEER clinical trial are:

1. To determine the safety and tolerability of T3D-959 in subjects with mild to moderate severity Alzheimer's disease
2. To determine the efficacy of T3D-959 on cognition and function in subjects with mild to moderate severity Alzheimer's disease
3. To identify plasma biomarkers of AD pathologies that may change in response to T3D-959 and determine their association with changes in cognition and function

METHODS

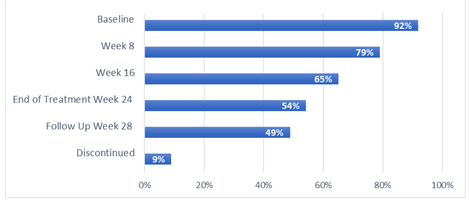
PIONEER is a randomized, double-blind, placebo-controlled, Phase 2 trial involving 256 mild to moderate AD patients (MMSE=14-26) dosed orally once-a-day for 24-weeks in 4 parallel arms (T3D-959 15mg, 30mg, 45mg and placebo QD in a 1:1:1:1 ratio). Co-primary outcome measures include the ADAS-cog11 cognition and global function ADCS-CGIC measures. Secondary outcome measures include DSCT and plasma Aβ 42/40 ratio. Exploratory outcome measures include plasma NfL tau, ptau217 and ptau181, apathy as measured by the NPI, expressive language function as measured by CFT, physical activity as measured by RAPA, plasma metabolomic and proteomic biomarkers and change in absolute regional, and whole brain, cerebral metabolic rate for glucose (CMRgl) as assayed by FDG-PET. [See ClinicalTrials.gov identifier NCT04251182].

Schedule of Assessments

	Baseline	Week 4	Week 8	Week 16	Week 24	Week 28
	Screening	Treatment			Follow-up	
Safety	X	X	X	X	X	X	X
Efficacy ADAS-cog11	X	X		X	X	X	X
ADCS-CGIC		X		X	X	X	X
DSCT	X	X		X	X	X	X
NPI - Apathy		X				X	
CFT	X	X			X	X	
GDS	X	X	X	X	X	X	X
Biomarkers – A/T/N		X	X	X	X	X	X
Biomarkers - Proteome		X	X	X	X	X	X
Biomarkers - Metabolome		X	X	X	X	X	X
Substudy – FDG-PET		X				X	
Substudy - PK						X	

RESULTS (as of 24 June 2022)

1. Study Progress – 74% complete, 32,000 treatment days complete



2. Patient Demographics

Summary of demographic characteristics

Characteristic	Total (N = 237)
Age*	72.7 ± 0.5
Female Sex (%)	147 (62.0)
Concomitant AD therapy (%)	96 (40.5)
Baseline HbA1c*	5.8 ± 0.03
Body Mass Index*	27.9 ± 0.3
Screening MMSE*	20.7 ± 0.2
Baseline ADAS-Cog11*	19.0 ± 0.5

* Values are means ± standard error of the mean

3. Safety

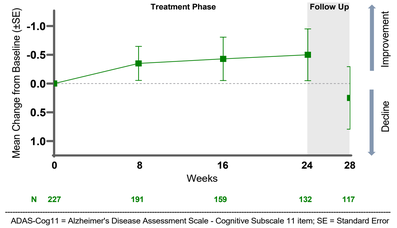
Number (%) of subjects with adverse events

	All adverse events	Related or possibly related adverse events
Any adverse event	70 (29.5%)	8 (3.4%)
Any serious adverse event	9 (3.8%)	0
Adverse event resulting in discontinuation	4 (1.7%)	0
Death	1 (0.4%)	0
Adverse events with incidence > 1%		
COVID-19	12 (5.1%)	0
Diarrhea	9 (3.8%)	3 (1.3%)
Urinary tract infection	9 (3.8%)	0
Fall	6 (2.5%)	0
Headache	5 (2.1%)	1 (0.4%)
Dizziness	3 (1.3%)	0

RESULTS (as of 24 June 2022)

4. Efficacy- ADAS-cog11– Blinded, All Dose Groups Averaged (Including Placebo)

ADAS-Cog11



ADAS-Cog11 = Alzheimer's Disease Assessment Scale - Cognitive Subscale 11 item; SE = Standard Error

Comparison To Aricept

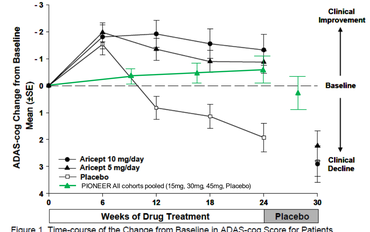
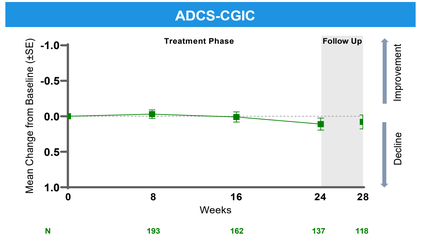


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

5. Efficacy- ADCS-CGIC– Blinded, All Dose Groups Averaged (Including Placebo)

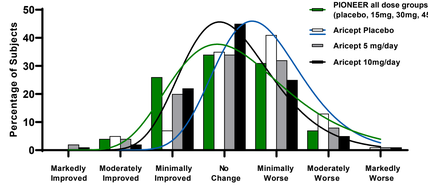
ADCS-CGIC



ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; SE = Standard Error

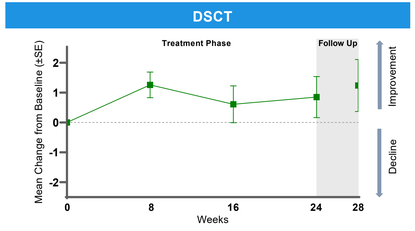
Comparison To Aricept

PIONEER CGIC vs. Aricept CIBIC+



6. Efficacy- DSCT– Blinded, All Dose Groups Averaged (Including Placebo)

DSCT



DSCT= Digit Symbol Coding Test; SE = Standard Error

CONCLUSIONS

1. PIONEER is 92% enrolled.
2. Topline results projected for 2Q2023.
3. Through 32,000+ treatment days T3D-959 appears to be safe and well tolerated.
4. Evidence of a possible treatment effect with improvement on cognition as assessed by ADAS-cog11 even with placebo data included in the all treatment groups average.
5. Evidence of a possible treatment effect with reduced decline on function as assessed by ADCS-CGIC even with placebo data included in the all treatment groups average.
6. Evidence of a possible treatment effect with improvement on executive function as assessed by DSCT even with placebo data included in the all treatment groups average.

REFERENCES

1. Tong, M., Dominguez, C., Didsbury, J. and de la Monte, S.M. (2016) Targeting Alzheimer's Disease Neuro-Metabolic Dysfunction with a Small Molecule Nuclear Receptor Agonist (T3D-959) Reverses Disease Pathologies. *J Alzheimers Dis Parkinsonism*, **6**.
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4. Chamberlain S, Gabriel H, Strittmatter W, Didsbury J. An Exploratory Phase IIa Study of the PPAR delta/gamma Agonist T3D-959 Assessing Metabolic and Cognitive Function in Subjects with Mild to Moderate Alzheimer's Disease. J Alzheimer's Dis. (2020) 73:1085-1103.

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