PIONEER, a Phase 2 Study to Evaluate Treatment with T3D-959 in Patients with Mild to Moderate Alzheimer's Disease: Study Design and Update

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Disclosures

JD, JS, SC and BS are full time employees of T3D Therapeutics and holders of stock/options

WS and HG are consultants for T3D Therapeutics and compensated for their time (including stock options)

PIONEER Trial Overview

- PIONEER is a Phase 2 randomized, double-blind, placebo controlled 24-week study in mild to moderate Alzheimer's patients testing the metabolic hypothesis of AD
- Assessment of an investigational new drug T3D-959, to correct both glucose and lipid metabolism aberrations in AD.
- Exploration of biomarker relationships to clinical manifestations of AD
- Trial re-started March 2021 after Covid-19 pandemic-related pause
- Trial is 50% enrolled (through Oct 2021)
- Topline results projected for 1Q 2023

T3D-959 Overview

- Primary target PPARδ (energy expenditure) and secondary target PPARγ (energy storage) are master regulators of metabolic homeostasis
- Unique PPAR selectivity profile convey a distinctive activity profile > central regulator of both glucose and lipid metabolism
- Unique molecule: Different structural class than the PPAR gamma-selective TZDs
- Only drug in development for AD with PPARδ as a primary target, a target found throughout the brain
- Orally delivered as a once-a-day capsule
- Brain penetrant
- Excellent safety profile
- Multiple efficacy signals in our previous exploratory Phase 2a AD study

Metabolism Hypothesis of AD

- Metabolic alterations (glucose and lipid) antedate structural change in AD brain
  - Brain – 2% of body weight
    - 25% of total glucose
    - 25% of total body free cholesterol pool
    - 20% of whole body oxygen consumption

- Decreased glucose metabolism is a cause not a manifestation of neurodegeneration
  - Decreased Glucose > decreased ATP > decreased ER/Golgi/Trans Golgi function > misfolded proteins (tangles and plaques)

- Aberrant lipid metabolism is a 3rd pathological hallmark of AD
  - Alois Alzheimer (1906) noted a high occurrence of “adipose inclusions” (fat deposits identified as triglycerides in 2015)
  - ApoE4 – strongest genetic risk factor

- AD involves a massive positive feedback loop of altered glucose/lipid metabolism alterations and pathological sequelae (plaques, tangles, inflammation)

PIONEER Design

- A Phase 2 randomized, double-blind, placebo-controlled design clinical trial.
- Evaluating three dose levels (15 mg, 30 mg, 45 mg) of T3D-959 vs. placebo in 256 subjects (64/arm) with mild-to-moderate Alzheimer's Disease (MMSE 14-26, CDR-Global 0.5-2.0 and CDR-SB $\geq$ 3.0).
- Subjects stratified by gender and ApoE4 genotype, assigned to one of four dose groups (1:1:1:1 ratio) in a randomized fashion.
- Study medication taken orally once daily for 24 weeks.
- Follow-up visit four weeks after the end of treatment.
- Approx. 40-45 US clinical trial sites

PIONEER Design – Outcome Measures

Primary

- Cognition – ADAS-cog11
- Function - ADCS-CGIC
- Safety and Tolerability

Secondary

- Executive Function – DSCT
- Amyloid Plaque Burden – Biomarker – Plasma Aβ42/40 ratio

Exploratory

- Apathy – NPI
- Expressive Language
- Physical Activity
- Brain Glucose Metabolism – FDG-PET scans
- Blood Biomarkers – Neurodegeneration, Tauopathy, Inflammation, Metabolism

PIONEER Design – Schedule of Assessments (General)

PIONEER Design – Cognitive Testing QC

VeraSci Inc. QC:

- Training and certification of raters
- Data review of screening eligibility assessments MMSE, CDR
- Data review of all Baseline and End of Treatment ADAS-Cog and CGIC, and percentage of DSCT

PIONEER Design – Plasma Proteomic Measures

A/T/N Biomarkers

- **5 Femtomolar (10^{-15} moles/L) proteomic biomarkers by LC/MS including NfL (N) and total tau (T)** (Inoviv, UK)
  - Selected from a list including NfL, BDNF, tau, IL18, Neurogranin
  - Significant development challenges for a multiplexed LC/MS assay
- **Phospho-tau 181 and 217 by LC-MS** (Inoviv, UK)
  - Promising AD specific plasma biomarkers complement AT(N)
- **PrecivityAD™ (or APTUS™ Aβ) to quantify Aβ42 and Aβ40 (A)** concentrations by LC/MS (C_2N Diagnostics, MO)
  - Clinical studies show that the APTUS™-Aβ test strongly predicts the presence of brain amyloidosis in a diverse population

Other

- **15 Picomolar or higher proteomic biomarkers by LC/MS** (Inoviv, UK)
  - Selected from a list of AD, inflammation, and metabolic biomarkers (adiponectin, TREM2)

PIONEER Design – Plasma Metabolomic Measures

- **HD4 Global Metabolomics**: Samples analyzed by Metabolon (**Durham, NC**) using their global untargeted LC/MS profiling platform
  - Over 800 metabolites will be monitored,
  - Building on Phase 2a and literature observations
  - Looking for systemic (peripheral) changes in fatty acid oxidation, branched chain amino acids, glutamine/glutamate ratio and ceramides

- **Complex Lipid Panel**: Concentrations of up to 1,125 lipid species for all four dose groups after 24 weeks.
  - Quantification of 14 Lipid Classes including: Ceramides, Sphingomyelins, Triacylglycerols, and Phosphatidylcholines
  - Measuring differences between placebo and active doses at the end of treatment
  - Examining changes in ceramides and plasmalogens observed in Phase 2a metabolomics

PIONEER Design – FDG-PET Sub-Study (N=8 per arm)

- Measuring **absolute rate** of glucose uptake and utilization in CNS before and after drug therapy
- Absolute CMRgl (ug/mL/min) values will be determined for multiple prespecified anatomical regions of interest (ROIs) - (BioClinica)
- Exploratory Voxel-wise (SPM) analysis (BioClinica)
- Baseline Hypometabolic Convergence Index (HCI) values (Banner AD Inst, AZ)

PIONEER Update (as of 31 Oct 2021)

A. Summary

- 41 Active US sites
- > 50% randomized (N=135)
  - Approx. 42% ApoE4 positive
  - Approx. 64% female
- Outcome measure variability consistent and well within assumptions

PIONEER Update (as of 31 Oct 2021)

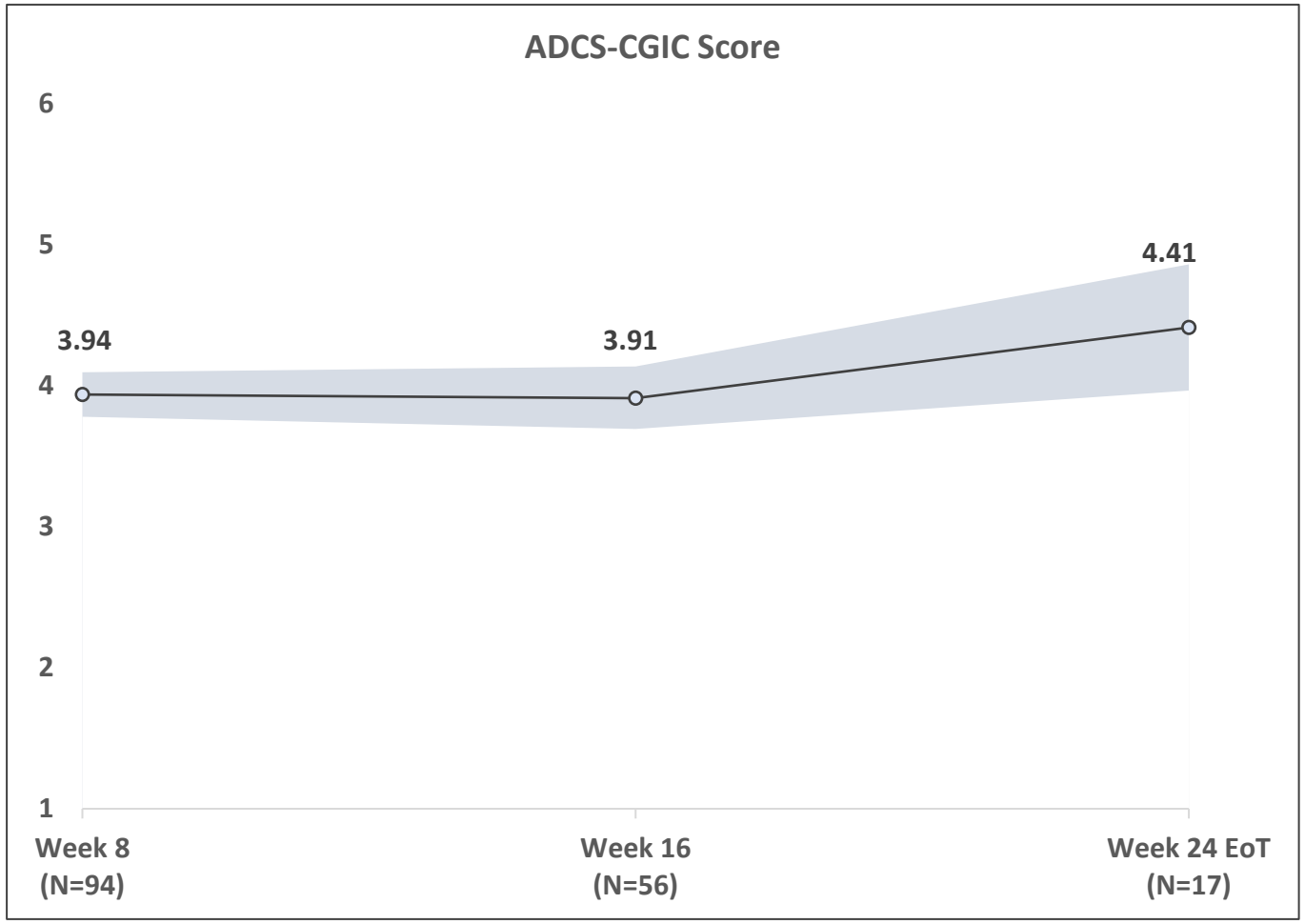
B. Safety – 135 Randomized Subjects

- 69 AEs across 33 subjects
- 1 treatment-related AE (bilateral foot cramps)
- No treatment-related SAEs [4 unrelated SAEs - seizure, hip fracture, arm fracture, vertigo/loss of peripheral vision]
- No deaths
- Two dropouts due to Covid-19 infection (subjects to be replaced)
- No dropouts due to treatment-related AEs
- No high frequency of any AE type

PIONEER Update (as of 31 Oct 2021)

C. Outcome Measures – CGIC [blinded summary, all groups combined, not final data]

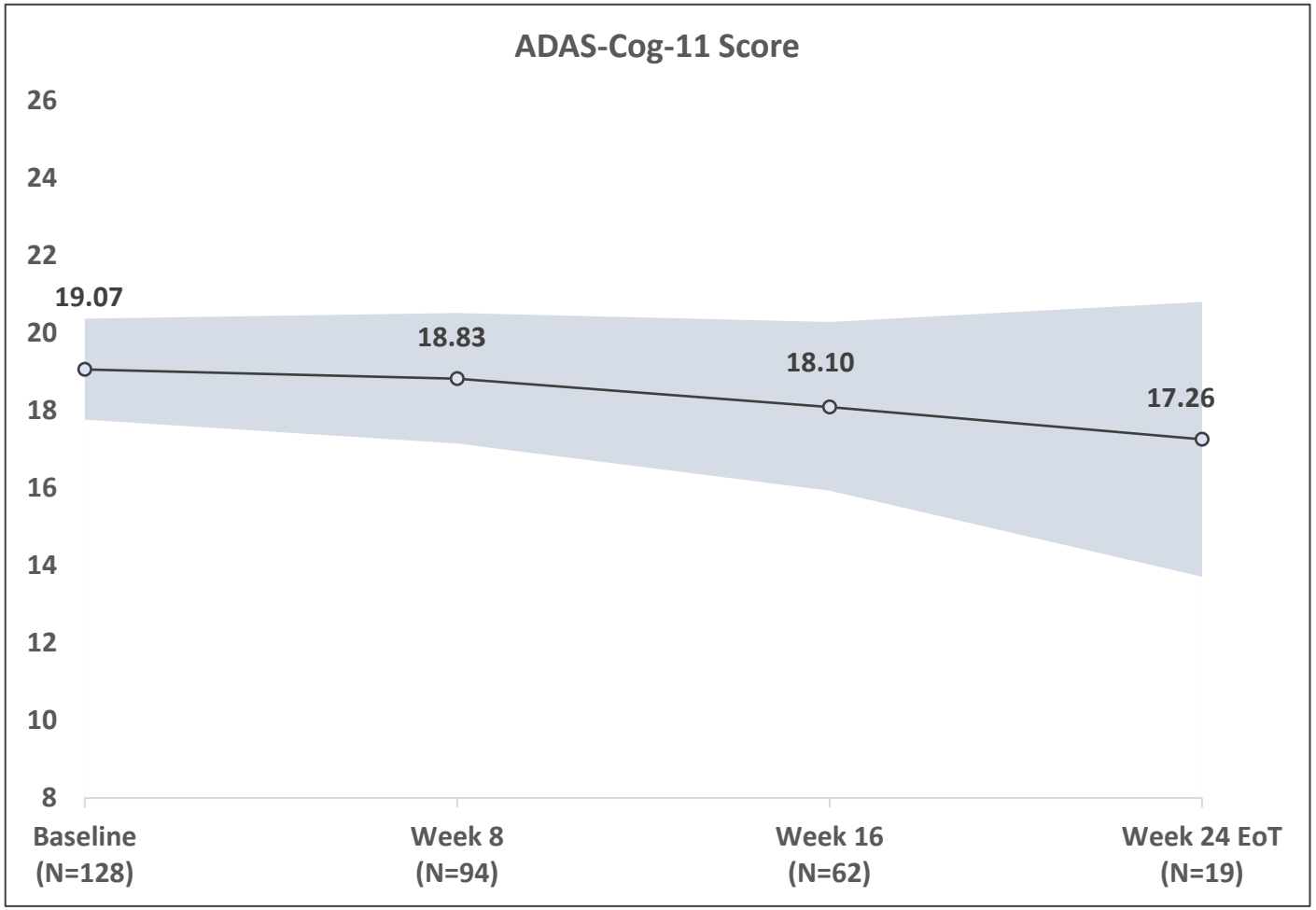
ADCS-CGIC			
	Week 8 (N=94)	Week 16 (N=56)	Week 24 EoT (N=17)
Average	3.94	3.91	4.41
max	6	6	6
median	4	4	5
min	1	2	2
N	94	56	17
SD	0.77	0.84	0.94
Upper 95% CI	4.09	4.13	4.86
Lower 95% CI	3.78	3.69	3.97



PIONEER Update (as of 31 Oct 2021)

C. Outcome Measures – ADAS-cog-11 [blinded summary, all groups combined, not final data]

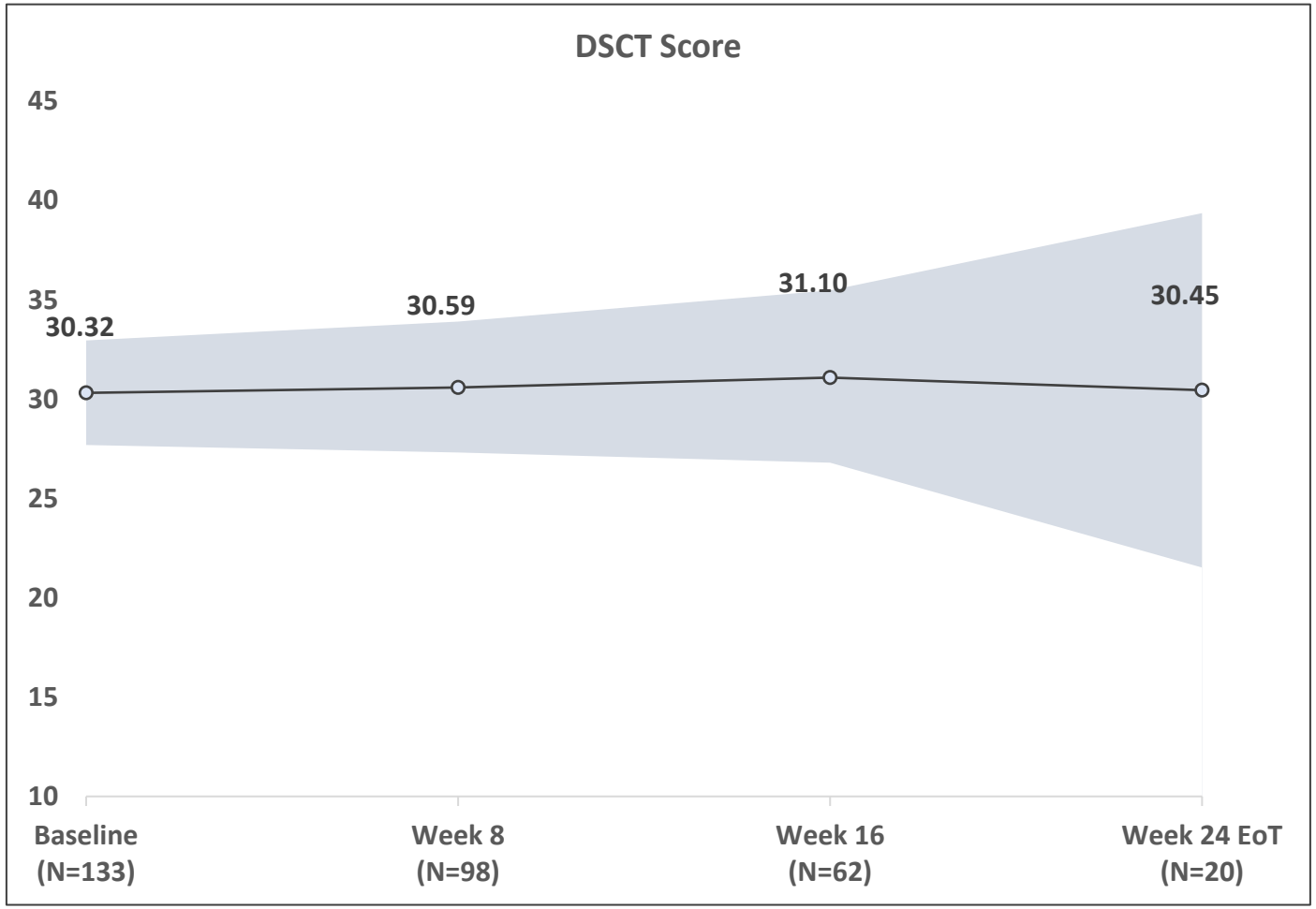
ADAS-Cog-11				
	Baseline (N=128)	Week 8 (N=94)	Week 16 (N=62)	Week 24 EoT (N=19)
Average	19.07	18.83	18.10	17.26
max	48	49	41	34
median	18	17.5	16	18
min	6	7	3	6
N	128	94	62	19
SD	7.49	8.28	8.68	7.89
Upper 95% CI	20.38	20.53	20.30	20.81
Lower 95% CI	17.77	17.16	15.94	13.71



PIONEER Update (as of 31 Oct 2021)

C. Outcome Measures – DSCT [blinded summary, all groups combined, not final data]

DSCT				
	Baseline (N=133)	Week 8 (N=98)	Week 16 (N=62)	Week 24 EoT (N=20)
Average	30.32	30.59	31.10	30.45
max	78	72	64	68
median	30	29	33	29.5
min	0	0	0	0
N	133	98	62	20
SD	15.38	16.54	17.23	20.36
Upper 95% CI	32.95	33.91	35.47	39.37
Lower 95% CI	27.70	27.32	26.81	21.53



PIONEER Update (as of 31 Oct 2021)

D. Projected Timelines

Activity	Duration (approx.)	Completion (approx.)
Enrollment	**14 months**	**2Q 2022**
Last Patient – Last Visit	**19 months**	**4Q 2022**
Database cleanup and lock	**20 months**	**4Q 2022**
Final Clinical Study Report	**22 months**	**1Q 2023**

SUMMARY

- The PIONEER Study is 50% enrolled
- No safety concerns to date
- Topline results projected for 1Q 2023

ACKNOWLEDGEMENTS

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