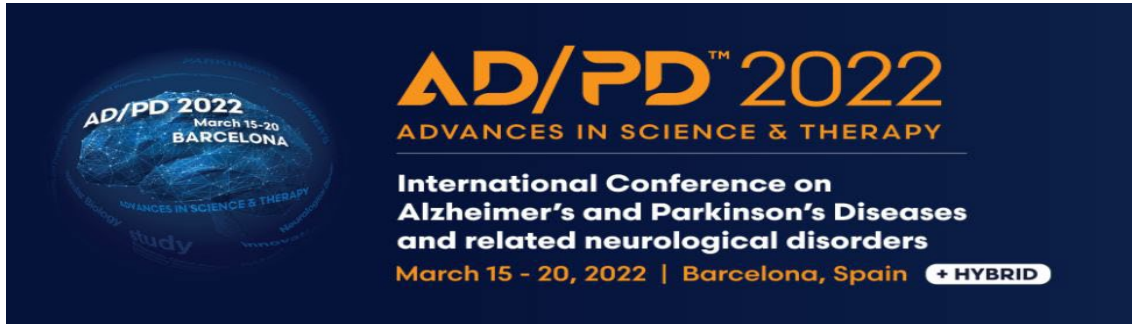
PIONEER, a Phase 2 Study to Evaluate Treatment with T3D-959 in Patients with Mild to Moderate Alzheimer's Disease: Study Design and Update

John Didsbury, PhD[1]; Jessica Stanek, PhD[1] ; Blake Swearingen, MS[1]; Stanley Chamberlain, PhD[1]; Warren Strittmatter, MD[1]; Hoda Gabriel, PMP[1]

(1) T3D Therapeutics, Inc., Research Triangle Park, NC,



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)

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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 72% enrolled (through 01 Mar 2022)
- Topline results projected for 2Q 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 conveys 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.
- PK and FDG-PET Sub-studies
- 35 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)
  - 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) - (Clario)
- Exploratory Voxel-wise (SPM) analysis (Clario)
- Baseline Hypometabolic Convergence Index (HCI) values (Banner AD Inst, AZ)

PIONEER Update - Summary (as of 01 Mar 2022)

- 35 Active US sites
- Enrollment ongoing
- 72% randomized (N=184)
  - Approx. 41% ApoE4 positive
  - Approx. 63% female
- Outcome measure variability consistent and well within assumptions

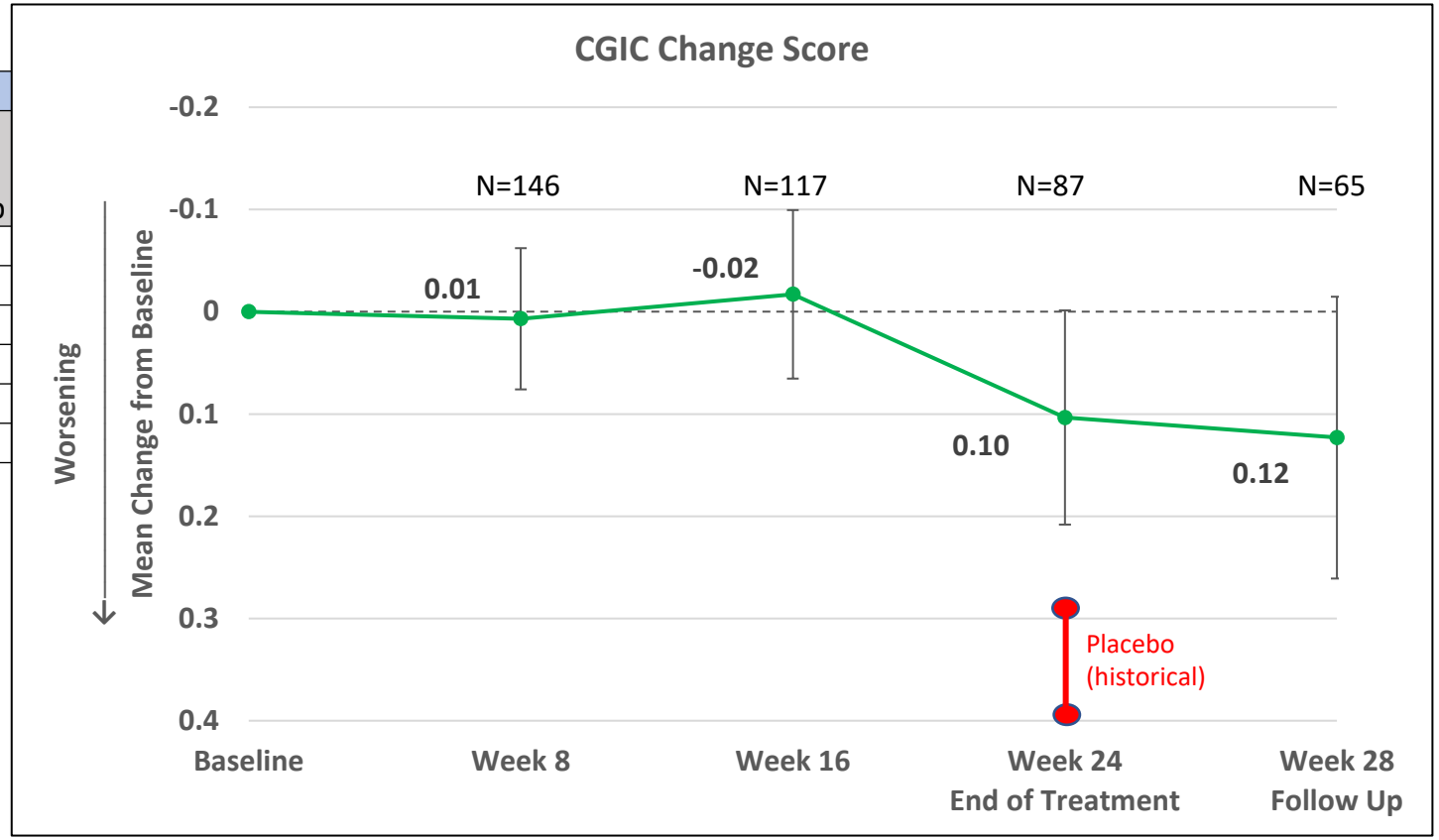
PIONEER Update - Safety (as of 01 Mar 2022)

- 184 randomized subjects representing >3,500 patient dosing weeks
- 152 AEs across 58 subjects
- 2 treatment-related AEs (bilateral foot cramps, loose stools)
- No treatment-related SAEs [11 unrelated/unlikely related SAEs - seizure, hip fracture, arm fracture, vertigo/loss of peripheral vision, giant cell arteritis, bladder cancer/postop complications, Bell's palsy, colitis, hypotension/fall/rib fracture, end stage dementia, heart attack]
- 1 unrelated death (end stage dementia)
- 2 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 – CGIC Outcome Measure (as of 01 Mar 2022)

For all Subjects Including Placebo

ADCS-CGIC Within Subject Change Score				
	Week 8	Week 16	Week 24 End of Treatment	Week 28 Follow Up
Average	0.01	-0.02	0.10	0.12
N	146	117	87	65
SD	0.83	0.89	0.98	1.11
SEM	0.07	0.08	0.10	0.14
Upper 95% CI	0.14	0.15	0.31	0.39
Lower 95% CI	-0.13	-0.18	-0.10	-0.15

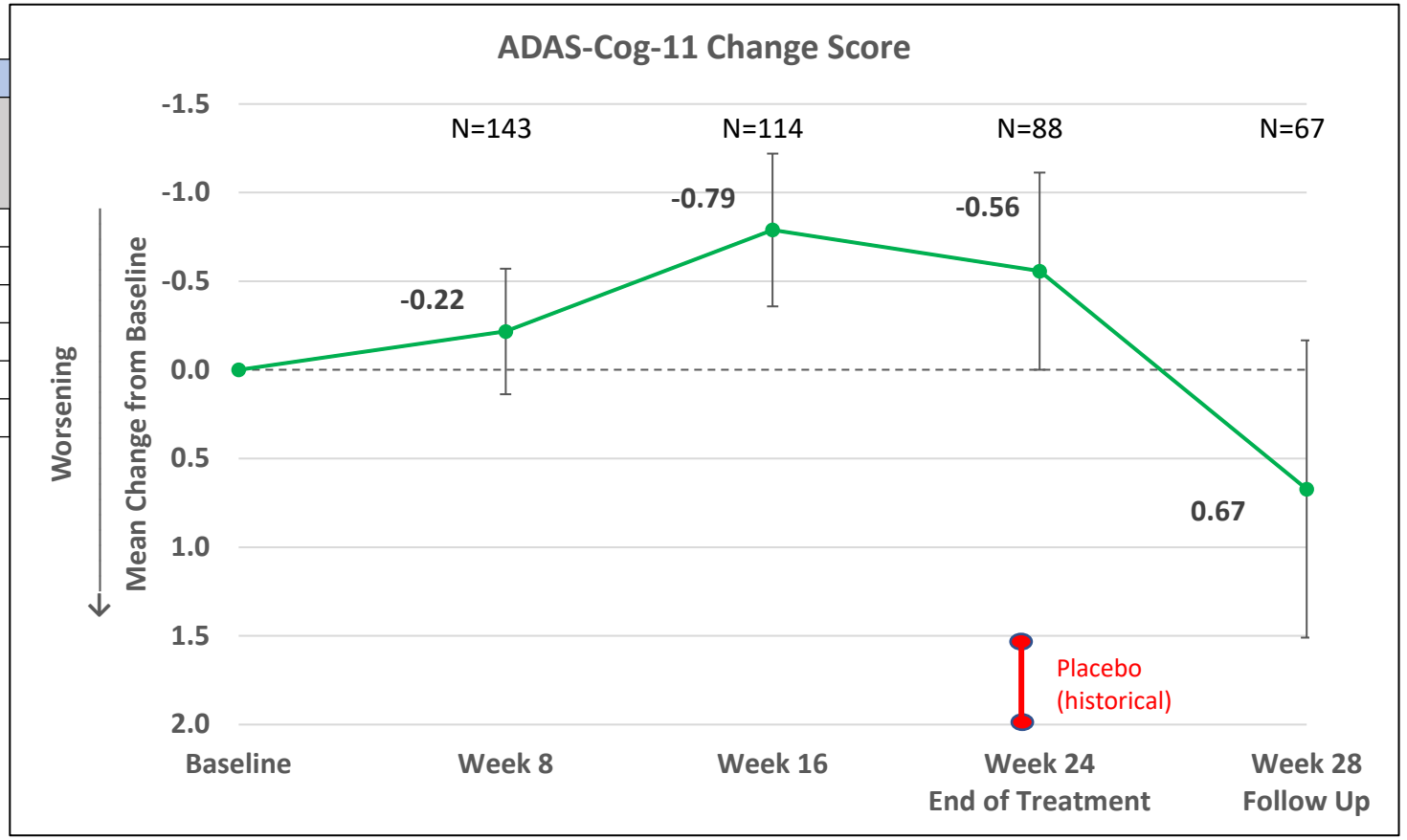


Green Line – Mean Score All Cohorts Combined
I-bars – Standard Error of the Mean

PIONEER Update – ADAS cog-11 Outcome Measure (as of 01 Mar 2022)

For all Subjects Including Placebo

ADAS-Cog Within Subject Change Score				
	Week 8	Week 16	Week 24 End of Treatment	Week 28 Follow Up
Average	-0.22	-0.79	-0.56	0.67
N	143	114	88	67
SD	4.23	4.60	5.21	6.86
SEM	0.35	0.43	0.56	0.84
Upper 95% CI	0.48	0.06	0.53	2.31
Lower 95% CI	-0.91	-1.63	-1.64	-0.97



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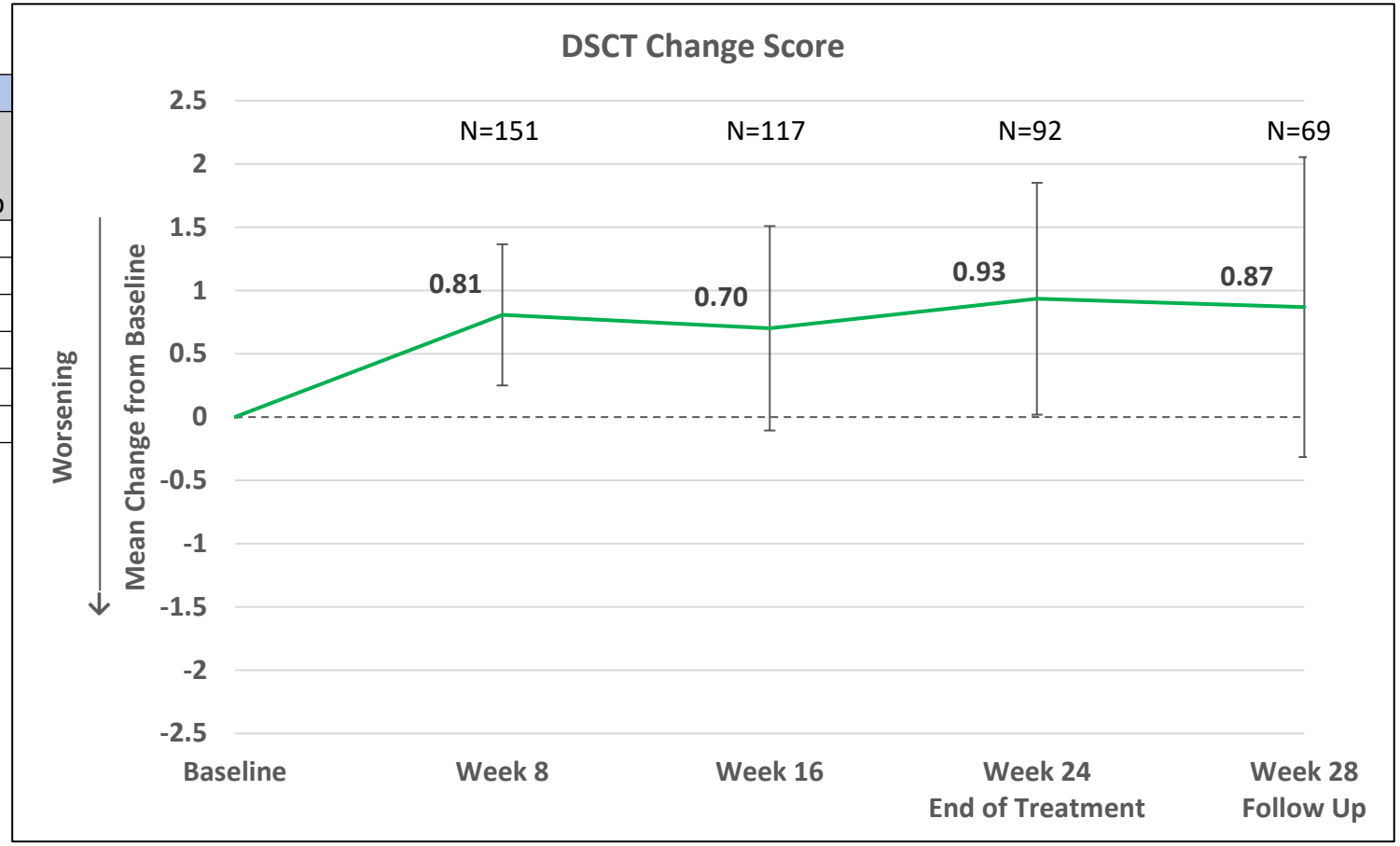
PIONEER Update – DSCT Outcome Measure (as of 01 Mar 2022)

For all Subjects Including Placebo

DSCT Within Subject Change Score				
	Week 8	Week 16	Week 24 End of Treatment	Week 28 Follow Up
Average	0.81	0.70	0.93	0.87
N	151	117	92	69
SD	6.86	8.73	8.79	9.85
SEM	0.56	0.81	0.92	1.19
Upper 95% CI	1.91	2.30	2.73	3.19
Lower 95% CI	-0.29	-0.88	-0.86	-1.45



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PIONEER Update – Projected Timelines (as of 01 Mar 2022)

Activity	Duration (approx.)	Completion (approx.)
Enrollment	16 months	3Q 2022
Last Patient – Last Visit	23 months	1Q 2023
Database cleanup and lock	24 months	2Q 2023
Final Clinical Study Report	25 months	2Q 2023

SUMMARY

- Evidence of a possible beneficial treatment effect of T3D-959 in mild to moderate AD patients.
- Average scores for all treatment groups combined (including placebo and possible sub-optimal drug strength arms) showing;
  - Improvement on ADAS-cog11 (cognition)
  - Improvement on DSCT (executive function)
  - Reduced decline in CGIC (global function)
- Excellent safety profile with no PPAR-related AEs
- The PIONEER Study is 72% enrolled
- Topline results projected for 2Q 2023

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