alzheimer's association
AAIC 20
ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®
July 27-31, 2020 > Virtual Event

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: RATIONALE AND STUDY DESIGN

JOHN DIDSBURY, PHD[1 †], WARREN STRITTMATTER, MD[1], STANLEY CHAMBERLAIN, PHD[1] AND HODA GABRIEL, PMP[1]

(1) T3D THERAPEUTICS, INC., RESEARCH TRIANGLE PARK, NC, USA

Disclosures

John Didsbury, Ph.D.

- Employee of T3D Therapeutics, Inc.
- Shareholder inT3D Therapeutics, Inc.

CME/CE credits will not be awarded for this presentation

.

alzheimer's association
AAIC 20

POLICIES

Photography is welcome in this presentation.

The information included in this presentation may be shared on other platforms.

Video and audio recording are prohibited.

Forward-Looking Statements

Statements contained in this presentation that are not statements of historical fact may be deemed to be forward looking statements. Without limiting the generality of the foregoing, words such as "may," "will," "expect," "believe," "anticipate," "intend," "could," "estimate" or "continue" are intended to identify forward-looking statements. Readers are cautioned that certain important factors may affect the Company's actual results and could cause such results to differ materially from any forward looking statements which may be made in this presentation or which are otherwise made by or on behalf of the Company. Factors which may affect the Company's results include, but are not limited to, product demand, market acceptance, impact of competitive products and prices, product development, commercialization or technological difficulties, the success or failure of negotiations and trade, legal, social and economic risks.

Takeaways

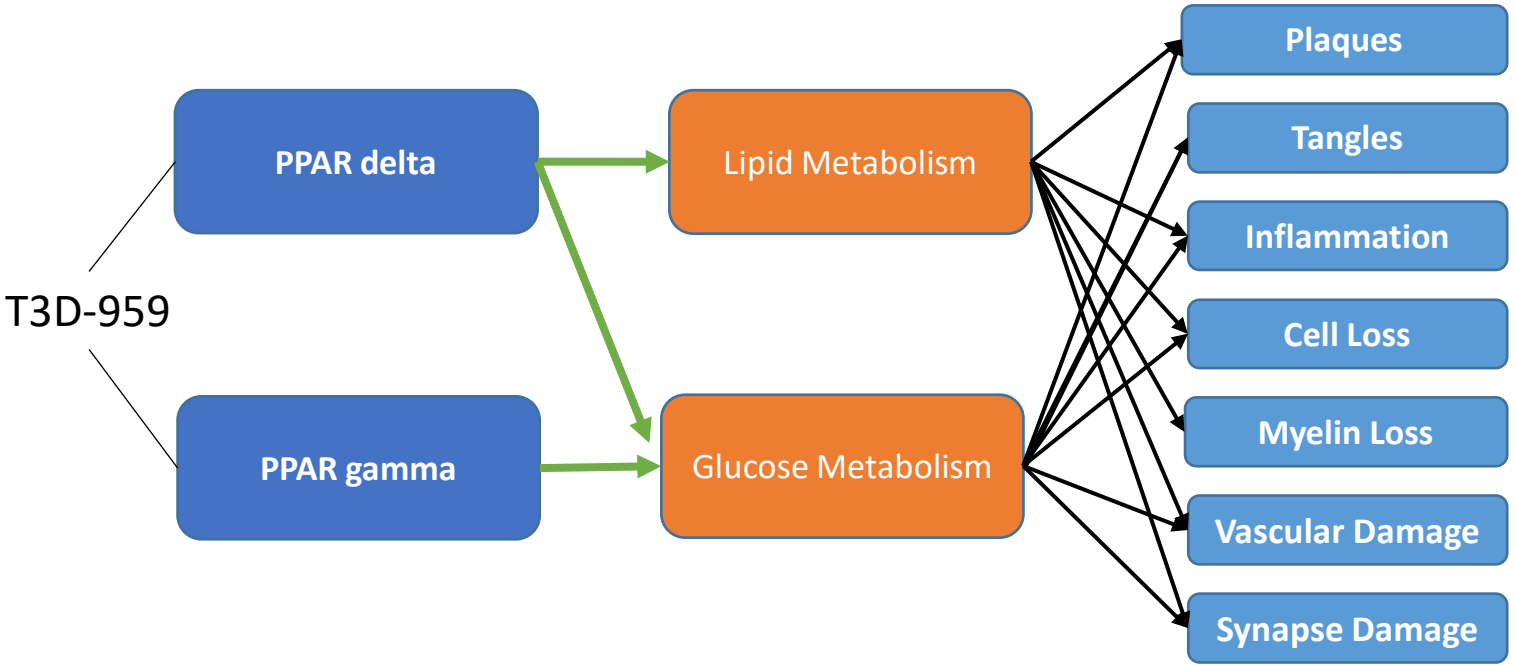
1. Assessment of a new drug T3D-959 to correct both glucose and lipid metabolism aberrations in AD. A robust test of the metabolic hypothesis for AD
2. Exploration of biomarker relationships to clinical manifestations of AD
3. A/T/N classification of AD – examination of drug-induced changes and relationship to cognition/function change
4. Novel trial adaptations in response to Covid-19

T3D-959

- PPAR delta and gamma dual nuclear receptor agonist
- Distinctly different than rosiglitazone or pioglitazone – chemically and biologically
- Regulating both glucose and lipid metabolism homeostasis
- Brain penetrant
- Oral delivery – once per day
- Multiple efficacy signals in exploratory Phase 2a AD trial
- Excellent safety profile

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: RATIONALE AND STUDY DESIGN

Aberrant Metabolism in AD



Phase 2a Exploratory Feasibility Trial – Mild/Moderate AD (NCT02560753)

- Excellent safety profile – No SAEs, 1 AE
- Metabolome changes dose-dependent systemic effects on lipid metabolism and metabolism related to insulin sensitization.
- Relative FDG-PET imaging demonstrated dose-dependent, regional, effects of T3D-959 on cerebral glucose metabolism.
- ADAS-cog11 and DSST cognitive assessments showed improvements with possible ApoE genotype association and pharmacodynamics related to the mechanism of drug action.

Phase 2 PIONEER Study (NCT04251182)

Design: Randomized, double-blind, placebo-controlled at 40-50 US sites

Objectives: Safety, Efficacy, Biomarkers

Subjects: Mild-to-moderate AD, MMSE 16-26, Age 50-90

Enrollment: 256 randomized, 64 subjects per treatment arm

Treatment Arms: 15mg, 30mg, 45mg T3D-959 & placebo. Stratified by ApoE4 genotype in a randomized fashion

Dosing: Once daily for 24 weeks with a 4-week post-dosing follow-up

Primary Objectives & Endpoints

1. Safety and tolerability
   - AEs, clinical labs, ECG, weight, vital signs
   - GDS (short form)
   - C-SSRS
2. Efficacy – Co-primaries
   a. ADAS-Cog11 from baseline to end of treatment visit
   b. ADCS-CGIC from baseline to end of treatment visit

Secondary Objectives & Endpoints

1. Evaluate the effect on beta amyloid plaque load as assessed by plasma Aβ 42/40 ratio biomarker level change from baseline to end of treatment visit

2. Change in executive function as assessed by Digit Symbol Coding Test (DSCT) from baseline to end of treatment visit

Exploratory Objectives & Endpoints

1. Effect on cognition and function – ADCS-ADL
2. Effect on apathy – NPI
3. Effect on expressive language function – Category Fluency Test (animals)
4. Effect on absolute regional, and whole brain, cerebral metabolic rate for glucose (CMRgl) as measured by dynamic FDG-PET in a subset of subjects (N=12/arm)

Exploratory Objectives & Endpoints

5. Prognostic potential of the FDG-PET Hypometabolic Convergence Index (HCI) observed at baseline to the changes in cognitive and functional responses to T3D-959 at end of treatment visit

6. Effect on plasma metabolomic and lipid metabolism biomarkers

7. Effect on plasma proteomic biomarkers
   - Inflammation
   - Metabolism
   - AD pathology

Exploratory Objectives & Endpoints

8. Effect on plasma tau (total tau, ptau181, ptau217)

9. Effect on plasma Nfl

10. Pharmacokinetics in a subset of patients

alzheimer's association
AAIC 20

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: RATIONALE AND STUDY DESIGN

Key Inclusion Criteria

- Male / female 50-90y
- Clinical diagnosis of mild-to-moderate AD (Stage 4 or 5) with MMSE= 16 - 26
- Neuroimaging evidence consistent with the diagnosis of AD
- Modified Hachinski $\leq$ 4 and CDR= 0.5 to 2.0

Key Exclusion Criteria

- Clinically significant psychiatric illness or neurological disease other than AD
- Clinical depression (GDS>6 at both screening and baseline)
- Glycosylated hemoglobin (HbA1c) $\geq$7.7 or unstable diabetes
- Clinically significant thyroid disease at screening TSH >5

Protocol Adaptations – COVID-19 "2nd Surge" Contingency

- Remote efficacy test administration at all clinic visits – 'laboratory setting'
  - rater and subject separated (2 rooms)
  - rater and subject connected via 'Zoom'-type Videocon interface
  - limited caregiver operational assistance (test equipment setup)

↓

Covid Contingency - clinical sites operationally compromised

↓

- Remote efficacy test administration – 'home setting'
  - home becomes the subject's clinic testing room
  - subject and caregiver already familiar with the testing process
- Safety assessments – home health care nurse

Protocol Adaptations – COVID-19 "2nd Surge" Contingency

- Consistency in data acquisition
- Opportunity to validate remote administration of CGIC test (& others)
- Limiting loss of data due to Covid-19

Summary of PIONEER

1. First robust test of the impact of correcting aberrant glucose and lipid metabolism in AD subjects with a new drug candidate, T3D-959
2. Supported by previous pre-clinical, Phase 1 and Phase 2a AD trial results and a major NIA grant (AG-061122)
3. Assessment of multiple biomarkers for their relationship to cognition and function
4. Novel trial adaptations in response to Covid-19