Towards a more representative Alzheimer's disease clinical trial: Ethnic differences in underlying pathology call for demographic consideration in drug label development

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INTRODUCTION

Alzheimer's disease (AD) clinical trials have historically underrepresented groups of racial and ethnic minorities – namely, the Hispanic/Latino population.[1] Hispanic Americans are the largest minority population within the United States,[2] and make up 18.5 percent of the country's total population.[3] Clinical trial samples with oversaturation of White, Non Hispanic/Latino participants exhibit poor external validity to the population of the United States.[4] These homogeneous samples limit the generalization of clinical trial results including efficacy and safety.[5] In a 1999 study, out of 185 new drug labels, 8% described differences in safety related to race. Only one out of 185 labels recommended dosage changes based on ethnic differences.[6]

The underlying pathology and safety profile of ethnic groups within samples are important factors in drug label development. The PIONEER Study is distinctive among AD clinical trials as it has a strong representation of Hispanic/Latino participants. Therefore, PIONEER is uniquely poised to investigate whether ethnic differences impact safety outcomes in an AD clinical trial, and if these differences warrant changes to drug label development.

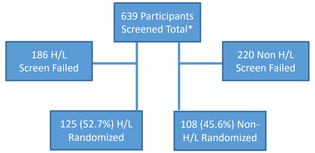
RESEARCH QUESTION AND OBJECTIVES

- Are there differences in screen fail data, safety profiles, and underlying pathology between Hispanic/Latino (H/L) and Non-Hispanic/Latino (Non-H/L) participants in the PIONEER trial?
- Evaluate differences between the ethnic sub-groups of the PIONEER trial.

METHODS

- PIONEER is a phase 2 randomized, double-blind, placebo-controlled design clinical trial
- 24-week study in mild to moderate Alzheimer's patients testing the metabolic hypothesis of AD
- Participants assigned to one of four dose groups (15, 30, 45mg, and placebo)
- T3D-959 is taken once a day orally for 24 weeks

Figure 1: Current Study Enrollment



*Study in progress – Figure 1 does not account for participants in screening

Figure 2: PIONEER Schedule of Visits and Assessments

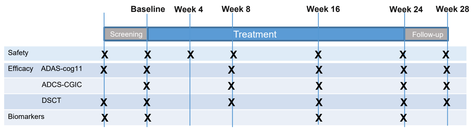


Table 1: Summary of demographic characteristics

Characteristic	H/L Participants (N = 125)	Non-H/L Participants (N = 108)	Total** (N = 237)
Age*	71.7 ± 0.7	73.7 ± 0.8	72.7 ± 0.5
Female Sex (%)	87 (69.6)	61 (56.4)	147 (62.0)
Concomitant AD therapy (%)	85 (68.0)	69 (63.9)	96 (40.5)
Baseline HbA1c*	5.9 ± 0.5	5.7 ± 0.04	5.8 ± 0.03
Body Mass Index*	29.3 ± 0.4	26.4 ± 0.5	27.9 ± 0.3
Screening MMSE*	21.2 ± 0.3	20.1 ± 0.3	20.7 ± 0.2

*Values are means ± standard error of the mean
**Four participants identified as an "Unknown" or "Not Reported" ethnicity

RESULTS

Screen Fails

Table 2: Screen Fail Reason by Ethnicity

Screen Fail (SF) Reason*	Hispanic or Latino (N = 125)	Not Hispanic or Latino (N = 108)
Did not meet Medication Stability and Washout Requirements	0	7
Significant Psychiatric Illness	1	0
Previous cardiovascular event	2	1
Blood pressure	2	4
Unstable Illness	1	3
Alcohol, drug use or dependence	4	2
Cancer within 5 years	0	1
Surgical or medical condition that may alter the absorption of any drug	1	0
Untreated clinical depression	7	11
Clinically relevant pathology	1	0
Covid-19	1	1
Neurological disease other than AD	2	3
HbA1c ≥7.7	22	2
Unstable diabetes	1	1
TSH > 5	2	3
Abnormal lab values	32	32
Positive HBsAg or HCV	1	3
Excluded Medications/Non-Drug Therapies	7	8
Medical Stability	2	3
No evidence of hepatic impairment or renal insufficiency	0	2

The SF rates for H/L and Non H/L participants are matched at approximately 60%. While most SF reasons are spread evenly across ethnic groups, two SF reasons stand out. No H/L participants (and seven Non-H/L participants) were screen failed as a result of not meeting Medical Stability and Washout requirements. In addition, 92% of screen fails due to abnormally high HbA1c values occurred in H/L participants.

Medical History

Figure 3: Medical History (MH) Events Differences by Ethnicity

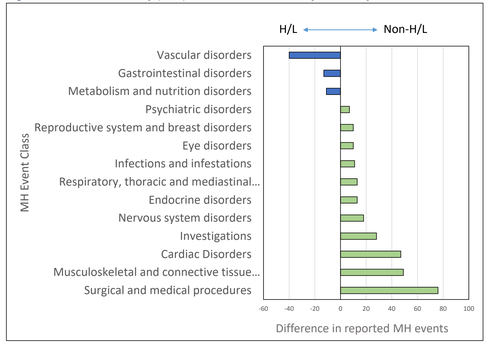


Table 3: Medical History by Ethnicity

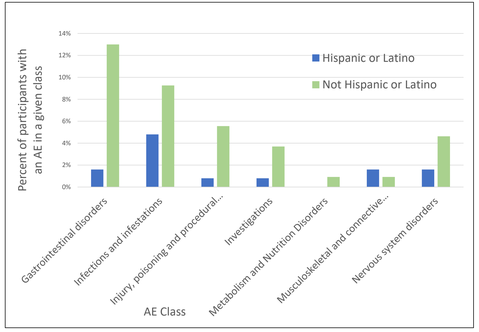
MH Event Class	Hispanic or Latino (N = 125)	Not Hispanic or Latino (N = 108)
Vascular disorders	115	75
Gastrointestinal disorders	79	65
Metabolism and nutrition disorders	129	117
Psychiatric disorders	63	70
Reproductive system and breast disorders	21	31
Eye disorders	28	38
Infections and infestations	20	31
Respiratory, thoracic and mediastinal disorders	40	52
Endocrine disorders	21	35
Nervous system disorders	47	66
Investigations	12	38
Cardiac Disorders	15	63
Musculoskeletal and connective tissue disorders	69	118
Surgical and medical procedures	133	204

*MH event classes with > 50 instances

- Non-H/L participants enter the PIONEER study with more medical history events than H/L participants.
- Non-H/L participants reported more cardiac disorders, musculoskeletal and tissue disorders, and surgical & medical procedures than H/L participants.
- H/L participants reported vascular disorder MH events at a significantly higher frequency than Non-H/L participants.

Safety Profile

Figure 4: Participants with Adverse Events (AE) by Ethnicity



- There are 19 (15.2%) H/L participants with at least one reported AE.
- There are 51 (47.2%) Non-H/L participants with at least one reported AE.
- There is an overall trend of Non-H/L participants reporting more AE's across medical categories of adverse events.

CONCLUSIONS

1. Despite a matched screen fail rate, H/L participants are more likely to screen fail due to abnormally high HbA1c.
2. The H/L community is known to have higher average HbA1c levels than Non H/L adults.[7] A high HbA1c level may be a sign of untreated diabetes. Because diabetes is an exclusion factor from many AD trials, it is important that physicians nationwide address chronic diabetes in the H/L population, to increase their representation in clinical trials.
3. H/L participants come onto the study with less medical history. Additionally, H/L participants may have a different medical history profile than Non-H/L participants.
4. Differences in the safety profile between H/L and Non-H/L participants may reflect a pattern of low reporting of adverse events in the H/L community.
5. The aforementioned ethnic differences are necessary considerations in design of more representative clinical trials. More diverse trials should consider the specific vulnerabilities of the H/L community
6. Future studies can place high priority on ethnic differences when analyzing participant safety data and developing drug labels. The inclusion of minority ethnic groups and races in clinical research is important, but it is only the first step in ensuring commercially available products are sensitive to and representative of these groups.

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