Use of a Novel Pharmacogenomic Biomarker to Enrich Responders to Liafensine in Treatment Resistant Depression (TRD) in a Phase 2b Clinical Trial (ENLIGHTEN)

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Methodological Question Being Addressed

Can a novel genetic biomarker platform identify a predictive pharmacogenomic biomarker for liafensine (a triple reuptake inhibitor) in patients with treatment-resistant depression (TRD), using clinical data and blood samples from prior clinical studies?

Introduction

Only subpopulations respond to treatment in most disorders

- **Diabetes** typical response rate is about 60%
- **Oncology** response rate as low as 25%.
- **Major depressive disorder**, approximately 35% of depressed patients are responsive to initial antidepressant (STAR-D)

Given diversity of drug responsiveness in patients

- Genetic biomarkers may identify responsive subpopulations
- Prior CNS drug trials may have failed because of heterogeneous study populations
- Post hoc identification of treatment response biomarkers from analyses of existing datasets may identify responsive subgroups
- Permits medications to be retargeted to responsive patients

Current work based on prior Phase 2b clinical development program for liafensine in TRD

- Prior studies failed to demonstrate liafensine superiority to standard-of-care antidepressant treatment (SOC) at Week 6

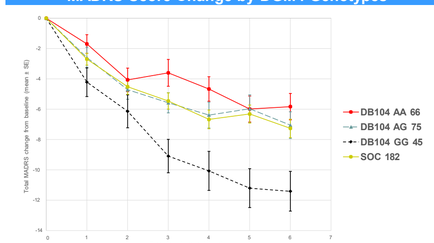
Methods

- GWAS was conducted using patient blood samples from prior Phase 2b studies
- Novel genetic biomarker single nucleotide polymorphism (SNP) DGM4 in ANK3 was identified
- New Phase 2b clinical trial using DGM4 to select patients was initiated (ENLIGHTEN Study)

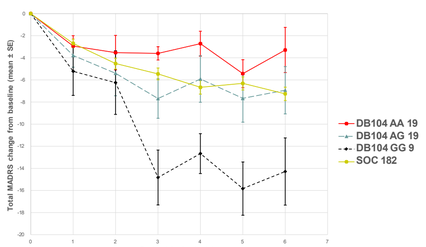
Results of Retrospective Analysis

- GWAS conducted using blood samples from prior Phase 2b studies
- Novel single nucleotide polymorphism (SNP) genetic biomarker identified (DGM4)
- DGM4 biomarker and MADRS data from TRD patients from prior Phase 2b studies found:
  - **GG genotype** exhibited **SIGNIFICANT** liafensine treatment effect compared to SOC at week 6
    - MADRS change from baseline: -12.4 ± 2.3 **liafensine** vs -7.7 ± 2.3 **SOC (p = 0.02)**
  - **AG and AA genotype** exhibited **NO** liafensine treatment effect compared to SOC at Week 6
    - MADRS change from baseline: -6.6 ± 1.0 liafensine vs -6.9 ± 1.0 SOC
  - **GG genotype exhibited NO** association with response to SOC duloxetine or escitalopram
    - MADRS -7.7 ± 2.3 in **GG group** vs -6.9 ± 1.0 in **AA and AG group** at Week 6

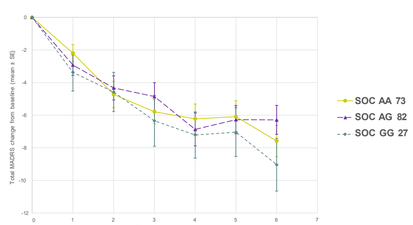
Biomarker DGM4 Discovery Set: MADRS Score Change by DGM4 Genotypes



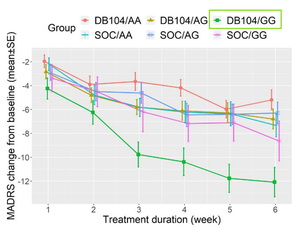
Biomarker DGM4 Validation Set: MADRS Score Change by DGM4 Genotypes



MADRS Score Change by DGM4 Genotypes in Control Arm (SOC: Duloxetine/Escitalopram)



MADRS Score Change in All Patients by DGM4 Genotypes

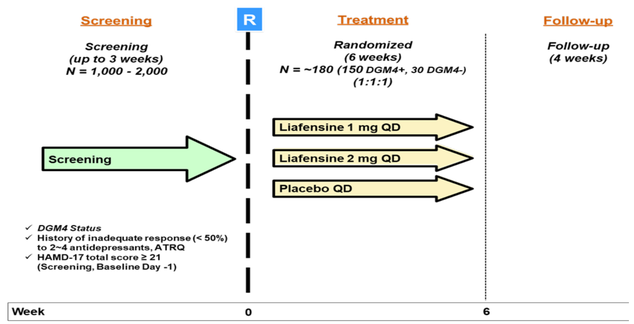


SOC (standard of care): Duloxetine/Escitalopram

Drug/Genotype	Patients (n)
DB104/AA	85
DB104/AG	94
DB104/GG	54
SOC/AA	73
SOC/AG	82
SOC/GG	27
Total	415

Ethnicity/Region	DGM4-positive (%)
Han Chinese in Beijing	21.4
European	18.1
Puerto Rican in Puerto Rico	9.6
Mexican descend in LA	4.7
African Ancestry in South West US	1.6

Ongoing Perspective ENLIGHTEN Study: A Global Phase 2b Biomarker Guided Trial



***ENLIGHTEN enrollment has been completed in Feb 2024**

Discussion

- This work represents an important step in developing a genetic biomarker for depression.
- Follow up studies required to support post hoc findings
- Validation study is ongoing
  - If study replicates post hoc findings, phase 3 pivotal studies will be initiated aiming for co-approval of liafensine for TRD and the DGM4 biomarker as a companion diagnostic test

Conclusions

- Successful confirmatory trials would be one of the first examples of biomarker-guided treatment selection of patients with TRD
- This work provides a model for identifying novel genetic biomarkers for other CNS drugs supporting personalized medicine for psychiatry and neurology

Disclosures

- All authors are employees of Denovo Biopharma or have received funding from Denovo Biopharma.