Use of a Pharmacogenomic Biomarker to Retarget a Failed Clinical Trial with DB104 (Liafensine) in Depression

Submission ID 3000470

SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Can a DGM (TM) genome wide scan platform designed to discover novel pharmacogenomic biomarkers be used to better target an optimal study population for drugs that have previously failed to demonstrate a significant treatment effect?

Introduction Variable clinical responses to medications likely reflect underlying genetic polymorphisms that differentially affect drug metabolism and/or phenotypic expression of the disease. Despite this generally accepted understanding, these polymorphisms have not yet been characterized and applied to clinical trials of CNS diseases. Absent this knowledge, study populations included in Phase 2 and 3 clinical trials represent heterogeneous mixtures of persons with multiple genetic polymorphisms some of whom may not be responsive to the study treatment or may be particularly sensitive to treatment side effects. This heterogeneity increases the variance in treatment response and diminishes the ability to detect significant clinical effects in the population that has been studied.
Selecting study populations with specific genetic profiles may allow the selection of persons into clinical trials who have a greater likelihood of positive treatment response and permit exclusion of persons who are particularly vulnerable to problematic adverse drug reactions. Once the product becomes available for clinical use, these same pharmacogenomic biomarkers could help clinicians apply a personalized medicine approach to persons most likely to have a positive treatment effect. Liafensine (DB104) is a potent, selective reuptake inhibitor of three monoamines, serotonin (5 HT), norepinephrine (NE), and dopamine (DA). This compound was previously evaluated (without success) as monotherapy for treatment-resistant depression (TRD). A biomarker was sought to identify a subpopulation of depressed persons who might find this treatment beneficial.

Methods Using archived samples from two DB104 Phase 2 studies, a genome wide scan was completed with the DGMTM platform to identify genetic biomarkers that correlated with DB104 efficacy. To prevent Type 1 errors driven by multiple comparisons, a p-value of 10-7 was required to establish a potential biomarker. The biomarker so identified was confirmed using the additional validation samples.

Results The DGMTM platform identified GM4 as a potential biomarker for liafensine treatment efficacy. Post hoc analysis of data obtained from prior Phase 2 work with liafensine showed that depressed patients with the DGM4 biomarker who were treated with liafensine demonstrated significant improvement on the MADRS ($p < 0.05$) as early as 2 weeks after treatment initiation compared to similar patients treated with placebo. Depressed patients without this biomarker failed to show this treatment differentiation. The result was confirmed in a separate validation set of samples.

Conclusion This study represents one of the first times genomic biomarkers have been used to personalize treatment for subsets of persons with depression who are most likely to be responsive to that treatment. DGM4 will be prospectively evaluated as a biomarker for effective treatment with liafensine in additional Phase 2 and Phase 3 clinical trials. Given the life long nature of depression and the poor outcomes that many experience with existing treatments, identifying target populations using genomic biomarkers that are likely responsive to a medication for treatment-resistant depressed persons would be an important public health advance in personalized medicine.
Lessons learned from this trial can inform drug development and help build towards better study designs that are more likely to have successful outcomes.
The current work has identified a specific polymorphism (SNP) that may permit detection of individuals likely to show clinical benefit to DB104. This biomarker will be used to select the study population in planned clinical trials for TRD.

Co-Authors

* Presenting Author

First Name	Last Name	Affiliation
Larry *	Alphs *	Denovo Biopharma
W	Luo	Denovo Biopharma
X	Lu	Denovo Biopharma
R	Alexander	Denovo Biopharma
H	Sun	Denovo Biopharma
H	Lu	Denovo Biopharma

Keywords

Keywords
Biomarkers
Personalized medicine
Treatment resistance
Depression
Treatment resistant depression

Guidelines I have read and understand the Poster Guidelines

Disclosures if applicable Support: Denovo Biopharma. All authors report potential conflicts as they are employees of Denovo Biopharma.

Related tables <blank>