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Pomaglumetad Methionil: A Case Study in Incremental Learning throughout Clinical Development

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Objectives

- Demonstrate how tailoring was incorporated into drug development
- Discuss key learning in designing a confirmatory multipopulation tailoring study

Outline

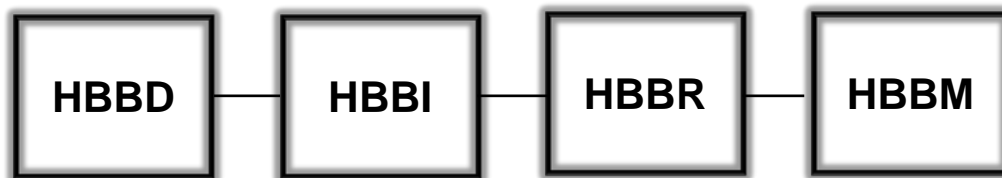
- Introduction
- Knowledge of biomarkers before the Phase 3 program
- Tailoring considerations for a Phase 3 study
- Key message

Introduction

- Pomaglumedad Methionil (Poma) was developed as a potential novel oral antipsychotic for the treatment of schizophrenia.
- Development for schizophrenia was stopped after Phase 3 studies failed to demonstrate efficacy in the population studied.
- Key learning from tailoring perspectives for Poma will be shared.

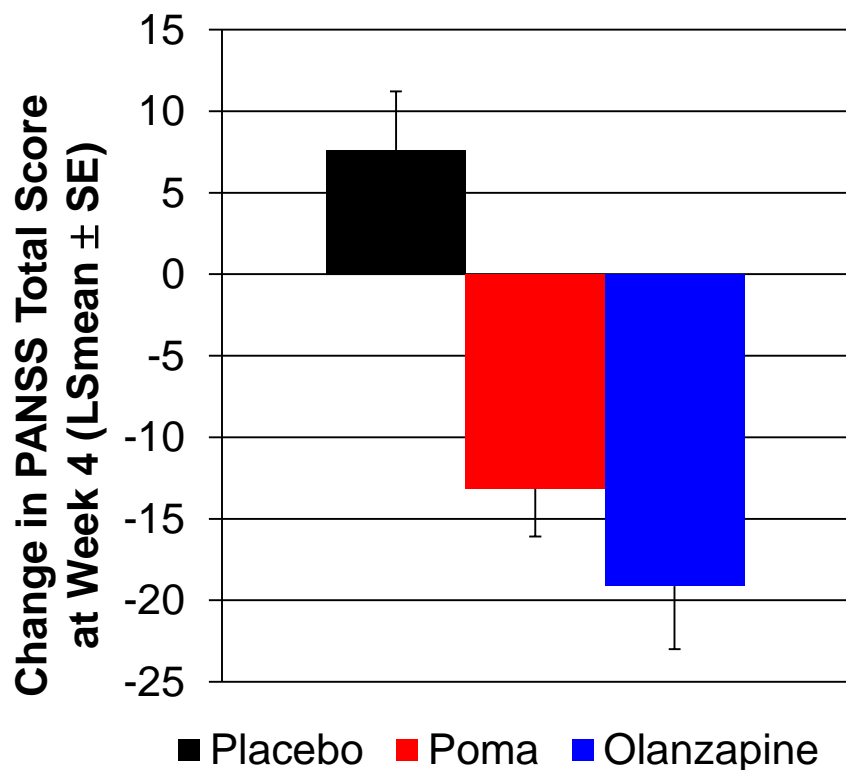
Key Poma Studies in This Talk

- **Study HBBD**
 - Phase 2 proof of concept (POC) study, placebo and active controlled
- **Study HBBI**
 - Phase 2 dose ranging study, placebo and active controlled
- **Study HBBR**
 - Phase 2 open label safety study, active controlled
- **Study HBBM**
 - Pivotal registration study, placebo and active controlled



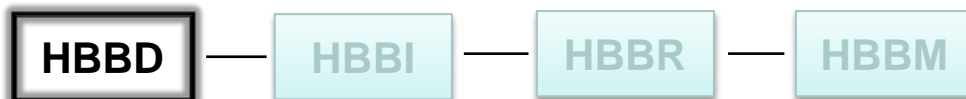
Knowledge of Biomarkers before the Phase 3 Program - Clinical Outcome from a POC Study

Study HBBD Clinical Outcome



- Significant separation of Poma from placebo ($P < 0.001$)
- Poma efficacy did not surpass olanzapine
- Results indicated a need for commercial differentiation

Note: data shown are contrasts based on MMRM models.



Knowledge of Biomarkers before the Phase 3 Program

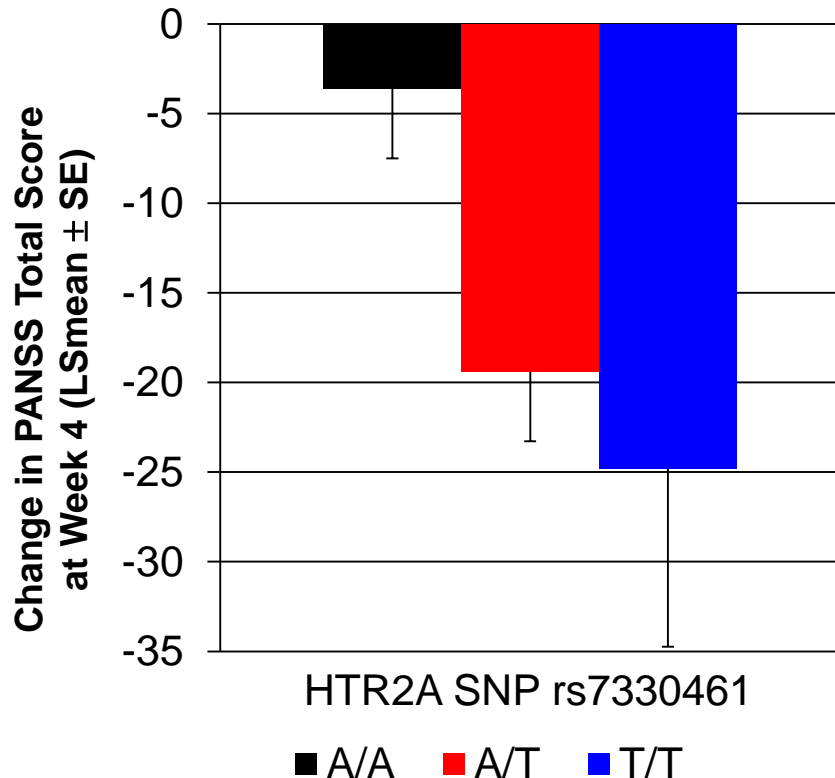
– Identify Tailoring Opportunity Using Genetics

- A pharmacogenetic (PGx)-based strategy was adopted.
- A retrospective candidate gene study was designed and conducted using samples from Study HBBD.

Knowledge of Biomarkers before the Phase 3 Program

– Genetic Analyses from the POC Study

Study HBBD Genetic Analysis in Poma Treated Patients



- Genetic markers potentially associated with Poma response
- HTR2A single nucleotide polymorphisms (SNPs)
 - NRG1 SNP

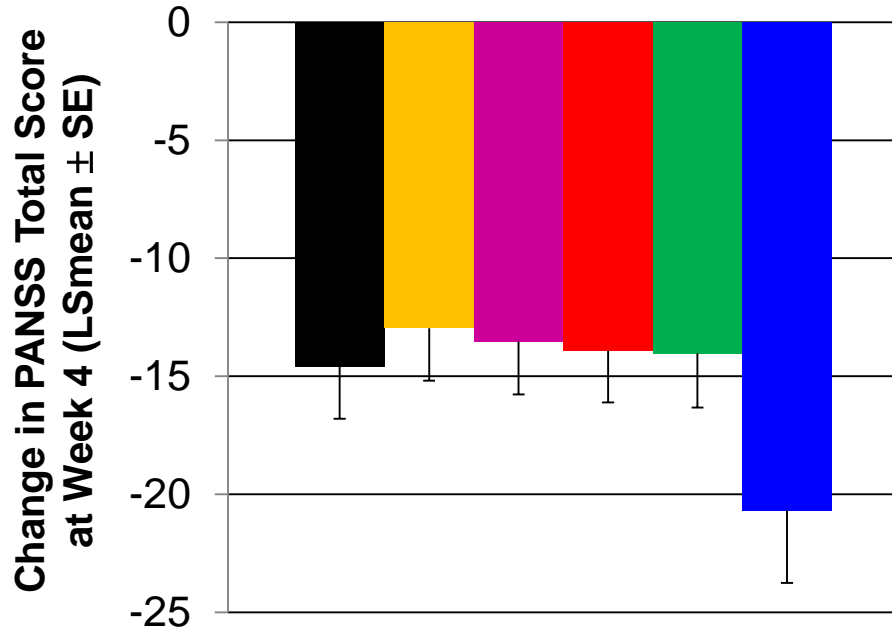
Note: data shown are contrasts based on MMRM models.



Knowledge of Biomarkers before the Phase 3 Program

– Planning for Genetic Analysis in Phase 2 study

Study HBBI Clinical Outcome



■ Placebo ■ Poma05
■ Poma20 ■ Poma40
■ Poma80 ■ Olanzapine

➤ Study HBBI was inconclusive.

- None of the 4 doses of Poma were more efficacious than placebo.
- The positive comparator, olanzapine, also failed to separate from placebo.

Note: data shown are contrasts based on MMRM models.



Knowledge of Tailoring before the Phase 3 Program - Genetic Analysis from Phase 2 Study

- Lack of full replication of Study HBBD genetic results
 - HTR2A SNP: Partial replication
- Because Study HBBI was inconclusive, the genetic analysis was also deemed inconclusive.



Challenge of Poma Clinical Development

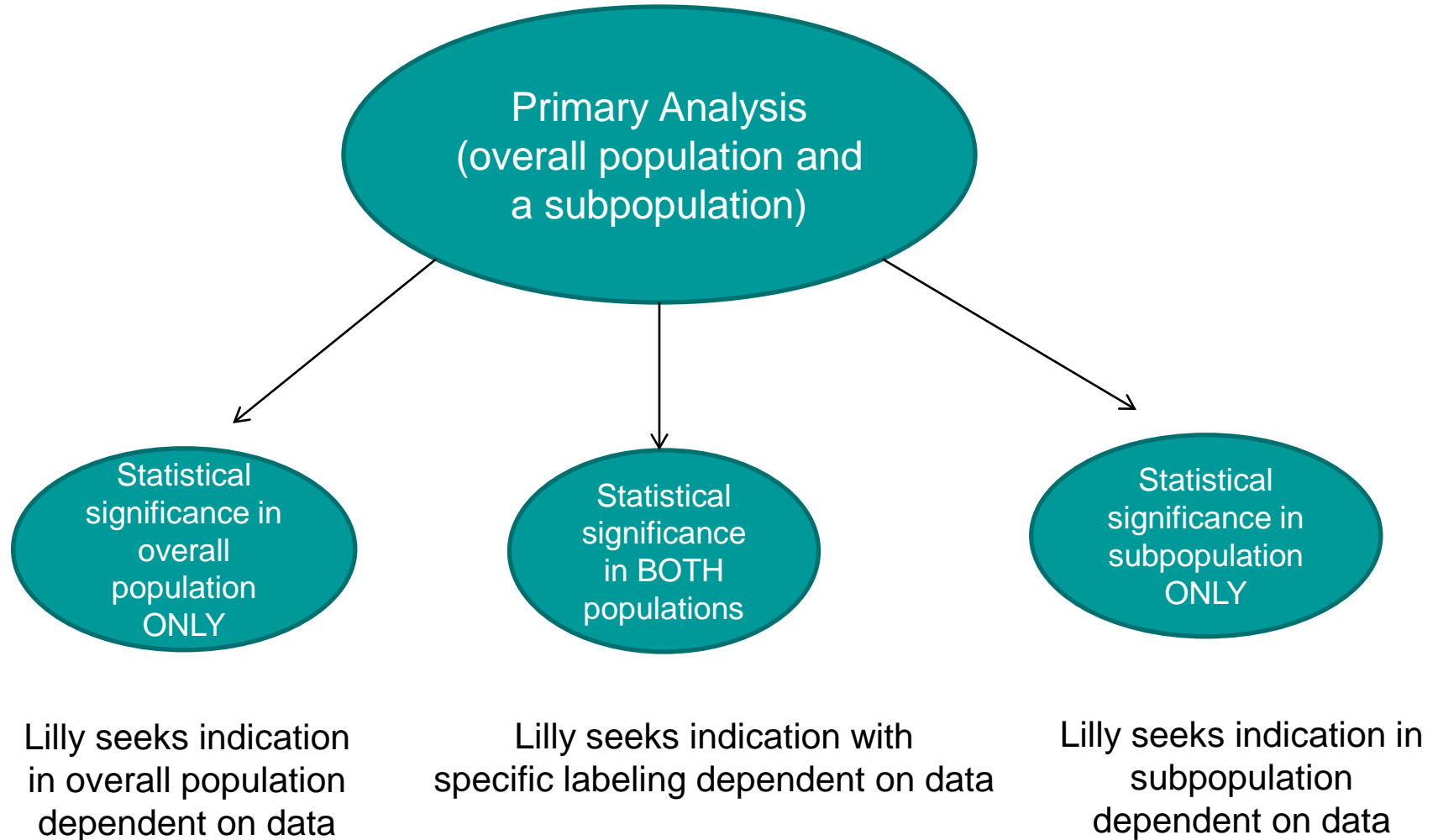
- **Development of antipsychotics difficult**
 - Study HBBI's inconclusive results likely were due to an unexpectedly high placebo response.
 - High placebo response contributes to study failures
 - Trend in increasing placebo response (Kemp et al. 2008)

- **New paradigm may be needed**
 - Current market necessitates the differentiation of new antipsychotics
 - Poma's novel mechanism of action (MOA) may provide a unique tailoring opportunity.

Study HBBM - Confirmatory Multipopulation Tailoring Study

- Incorporate tailored therapy opportunity in pivotal studies
- Continue to pursue the possibility of an all-comers treatment (ie, overall population and a predefined subpopulation)

Potential Clinical Outcome Scenarios for Study HBBM



Tailoring Considerations for the Phase 3 Study - Defining the Subpopulation for HBBM

➤ Questions:

- Define 'tailored' population based on a single SNP or multiple SNP's?
- What's our level of confidence in these results?

➤ Context:

- HTR2A signal: noted in 2 independent studies, one of which was inconclusive

Tailoring Considerations for the Phase 3 Study - Approach to Define the Subpopulation

- Extract information from Studies HBBD and HBBI (genotype frequencies, genetic effect)
- Quantitative assessment for each option (size and effect size)
- Extensive simulation work to assess $p(\text{TS})$ under each option
 - For multiple SNP definitions, also evaluated assuming one component was null.

Tailoring Considerations for the Phase 3 Study - Decisions for the Subpopulation

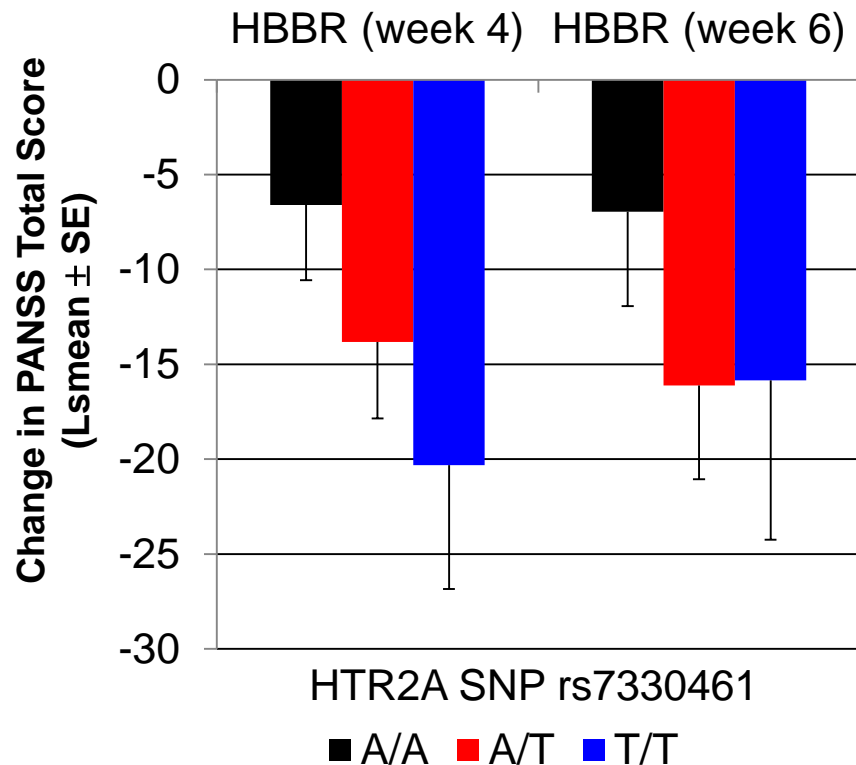
- Defined using composite markers based on genotypes of two SNPs
 - size of subpopulation: 45% of overall population
 - randomization was not stratified based on subpopulation status
- Subpopulation defined in protocol before study starts due to the Food and Drug Administration's (FDA's) recommendation.

Registration Study HBBM: Confirmatory Multipopulation Tailoring Study

- The primary objective of this study is to test the hypothesis that at least 1 dose level of LY2140023, 80 mg BID or 40 mg twice daily (BID), will demonstrate significantly greater efficacy than placebo at Visit 9, in one or more of the following populations:
 - the overall schizophrenia population; and
 - a predefined subpopulation of patients.
- The primary objective will be tested using a fallback testing methodology which provides strong control of the Type I error rate at the 1-sided 0.025 level.

Additional Information as Phase 3 Study Was Ongoing – Genetic Analyses from Study HBBR*

Study HBBR Genetic Analysis in Poma Treated Caucasians



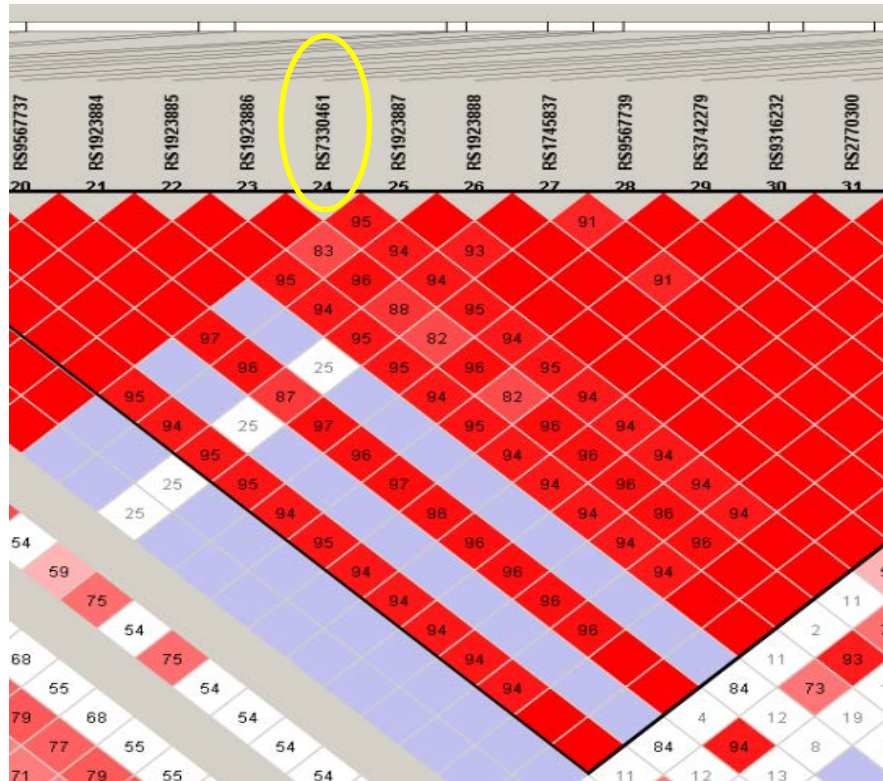
➤ HTR2A SNP:

- replicated in Caucasians
- ambiguous in African Americans (n=35)

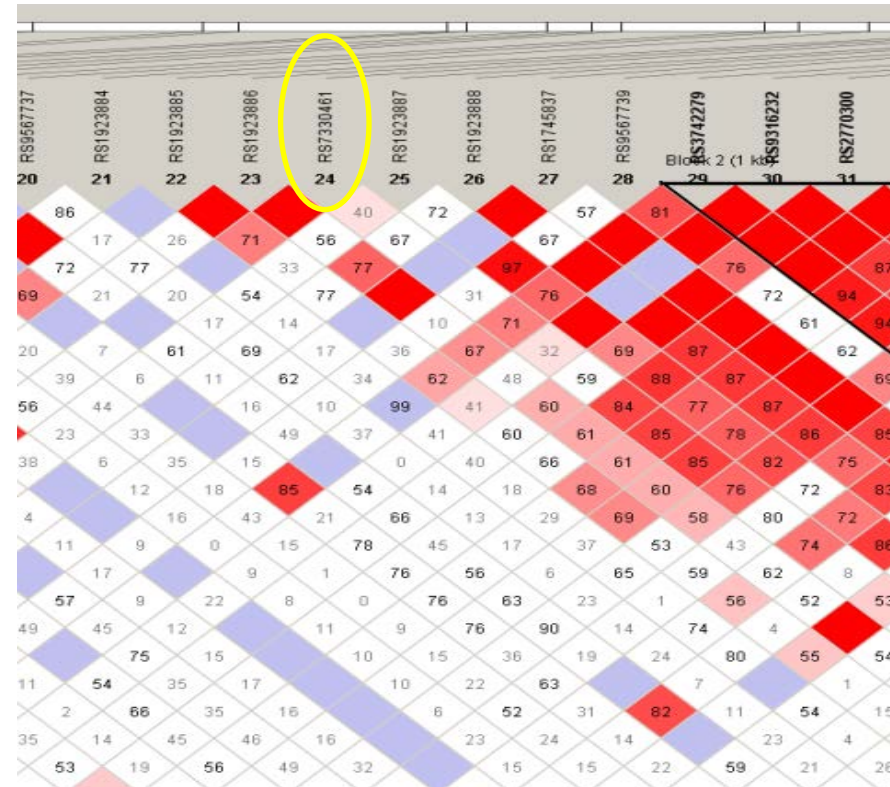
Note: data shown are contrasts based on MMRM models.



Study HBBR Provides First Opportunity to Study HTR2A Genetic Effect in African Americans



White Caucasian



African American

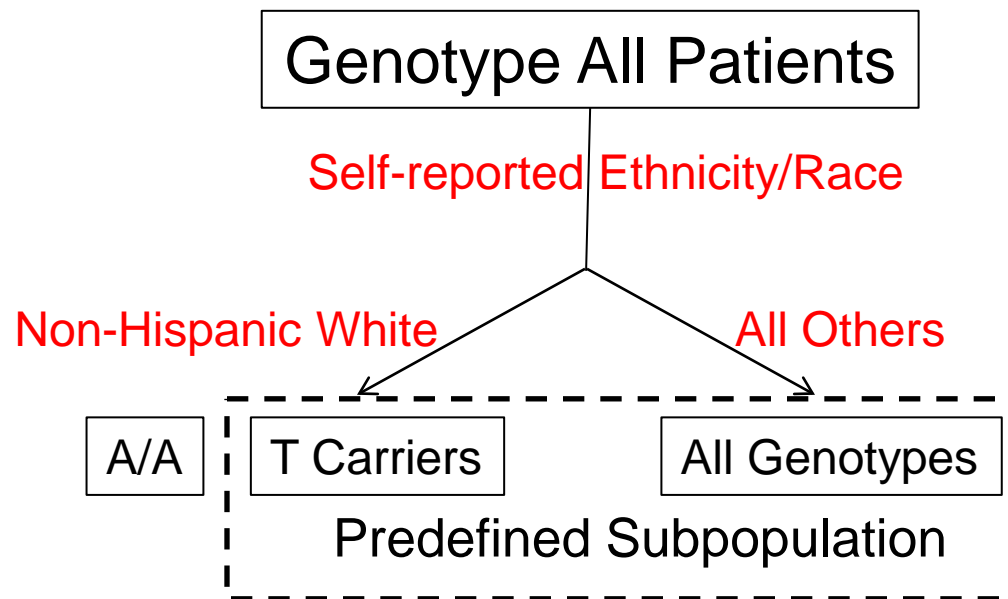
Linkage disequilibrium is different between ethnicities.
As a result, Phase 3 study designs need to be modified.

Considerations for Redefining the Subpopulation in Study HBBM

- Only HTR2A SNP remains of interest
- Genetic effect is race (ie, Caucasian) specific
- Subpopulation size depends on geographies used in study
- Practicality and ease of use for practitioners is considered
- Probability of study success based on study size, overall effect size, size of subpopulation (relative to overall) and assumed effect size for subpopulation
 - Pr(of Poma separating from placebo in at least one population in study)
 - Pr(of Poma separating from placebo in subpopulation | no separation in overall population)

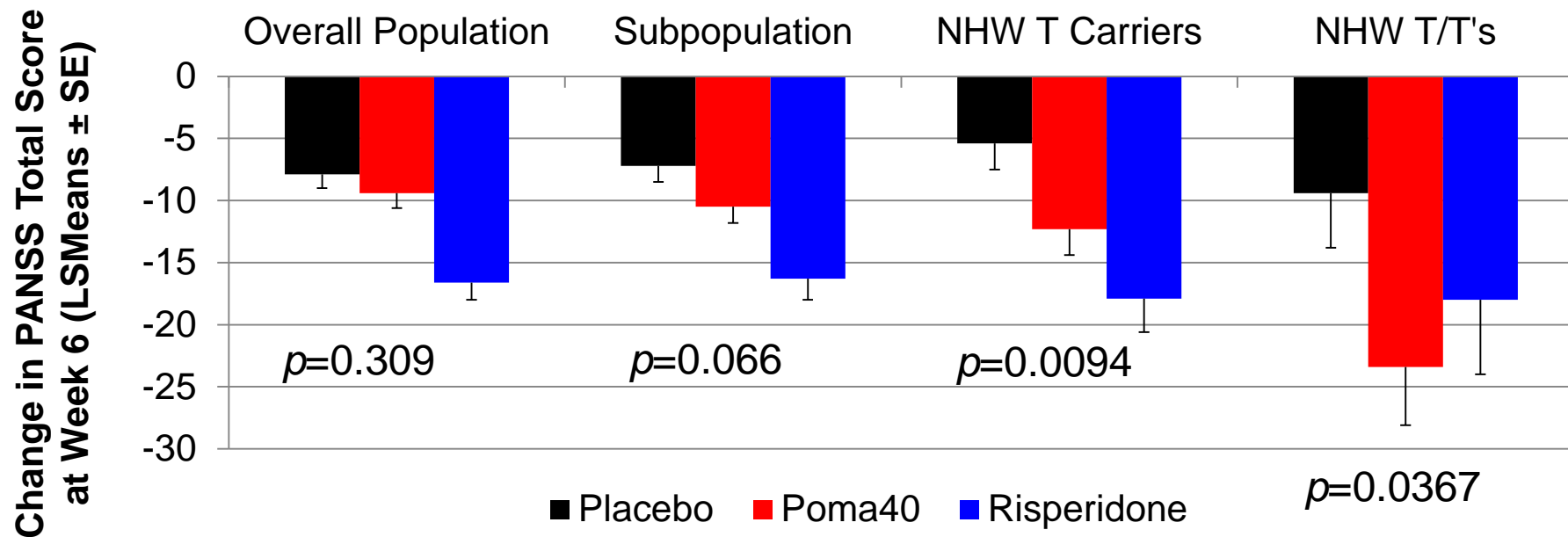
Study HBBM Predefined Subpopulation Based on Genetic Biomarker and Race

Predefined Subpopulation Composition



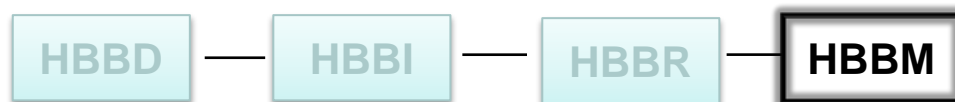
T Carriers and A/A: genotype for HTR2A SNP rs7330461

Study HBBM Clinical and Genetic Analysis Outcome



- Overall and predefined subpopulations: no significant efficacy in patients treated with Poma
- Non-Hispanic White (NHW) T Carriers and T/T's: significantly greater improvement in patients treated with Poma 40 mg BID (2-sided $p < 0.05$)

Note: data shown are contrasts based on MMRM models. All p-values are Poma40 versus placebo.



Key Messages

- It is critical to incorporate tailoring hypotheses early in clinical development.
- Tailoring is an ongoing and incremental learning process, study designs may be influenced by new data.
- Tailoring requires collaboration of many functions and statistics could provide leadership in this process.

Open Questions for Discussion

- What are some recommended approaches to quantify level of confidence for subgroup data?
- Timing of defining subpopulation
 - Prespecify prior to study starts or can we specify in the Statistical Analysis Plan when we have more data?
- Refinement of subpopulation postmarket
 - Do we test broader population and remove as data suggests, or do we start with smaller population and add in more patients?
- Others?

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