

Exposure-response analysis of minzasolmin in Parkinson's disease using a lean fit for purpose approach to inform decision making

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Objectives

To understand the relationship between minzasolmin exposure and efficacy endpoints using a fit for purpose approach to inform dose selection for potential phase 3 studies.

- MDS-UPDRS total score (clinical score for evaluating Parkinson's disease)
- MDS-UPDRS part III (assessment of motor symptoms) sub-scale
- Time to worsening of the MDS-UPDRS score
- Time to initiation of symptomatic therapy
- Changes in the DaT-SPECT mean striatum specific binding ratio.

Background

- Minzasolmin: Oral inhibitor of alpha-synuclein (ASYN) misfolding and aggregation.
- Aggregated ASYN : hallmark fibrillar protein deposits of Parkinson's disease.
- ORCHESTRA Study⁽¹⁾: Phase 2 PoC to test minzasolmin's efficacy at 180 mg (90 mg bid) and 360 mg (180 mg bid) daily doses.
- Primary Objectives: Assess clinical symptoms of disease progression over 12 and 18 months.
- Secondary Objectives: Effect on neurodegeneration of dopaminergic neurons and symptomatic treatment (ST) intake.
- Primary analysis⁽²⁾: no significant effect on the primary endpoint nor on any of the secondary clinical endpoints. An effect on DAT-SPECT was observed at 12-months.

Methods

Study Design

- Double-blind, placebo-controlled, randomized Ph2a study
- 18 months, 496 participants
- Minzasolmin 90mg bid and 180mg bid, placebo
- MDS-UPDRS total score : 4481 assessments from 490 subjects

Study Assessment and StatisticalAnalyses

Classical cross-sectional and longitudinal statistical linear mixed effect models, incorporating treatment effect, drug exposure, and the initiation of symptomatic therapy where relevant.

Results

MDS-UPDRS scores : no treatment effect

- No difference between the treatment groups.
- No exposure-response observed.
- No change in the slope of the score with drug, with or without initiation of symptomatic therapy.
- No decrease in the time to worsening with drug.

Time to start symptomatic therapy

- No treatment effect, no exposure-response observed.

DAT-SPECT

- Statistically significant association between minzasolmin exposure and changes in DAT-SPECT is observed, but this association decreased at month 18 compared to month 12.

Conclusions

Early identification of the lack of exposure-response relationships and the drug's superiority over placebo.

The use of longitudinal linear statistical models allowed for rapid delivery of results.

Given the endpoints and short timeframe, it would likely not have been possible to achieve these results using more complex models.

MDS-UPDRS total score



$$Y_{ij} = \alpha + \beta_1 * SEX_i + \beta_2 * AGE_{gr_i}^{(3)} + \beta_3 * Time_{ij} + \gamma_1 * Time_{ij} * TRT_i / PK_i^{(4)} + \gamma_2 * ST_{ij} + Error_{ij} \text{ for subject } i \text{ at time } j$$

- The MDS-UPDRS is a comprehensive tool for evaluating Parkinson's disease.
- It includes assessments of motor and non-motor experiences of daily living.
- The score is divided into four parts: Part I, II, III, and IV.
- Part III focuses on motor examination and part II on the emerging symptoms.
- Higher scores indicate more severe symptoms.

Figure 1 Obs. total score by treatment and visit

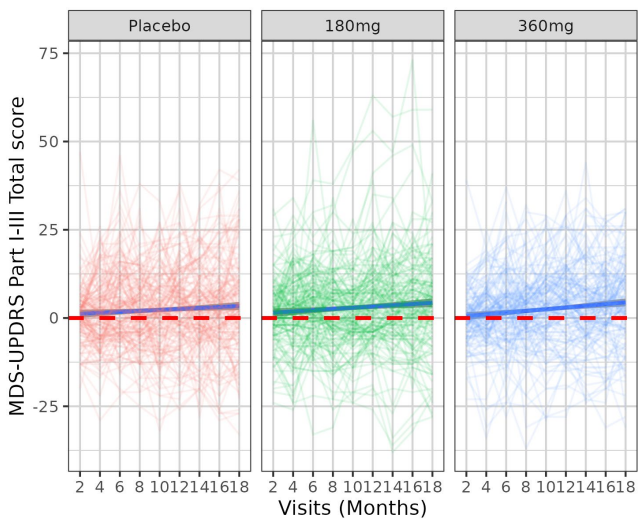


Figure 2 Obs. change from baseline at month 12 by treatment and onset of ST

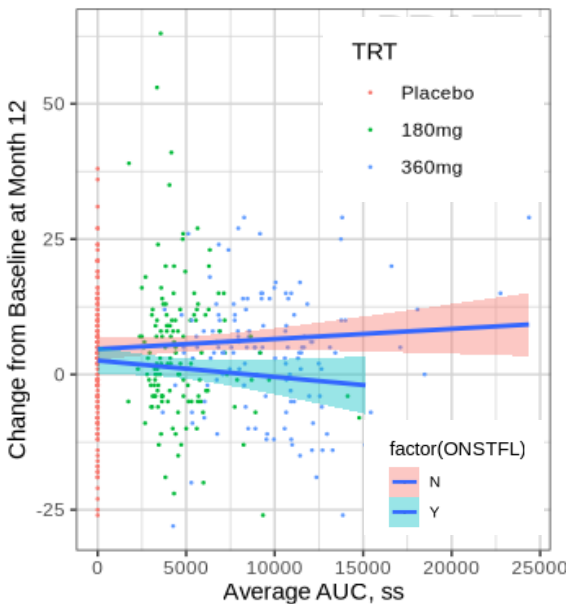


Figure 3 Obs. probability of ST start by months

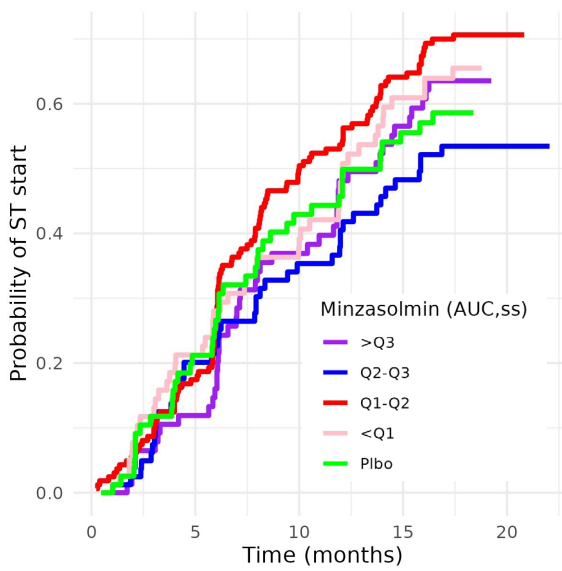


Figure 4 Pred. total score by treatment and visit

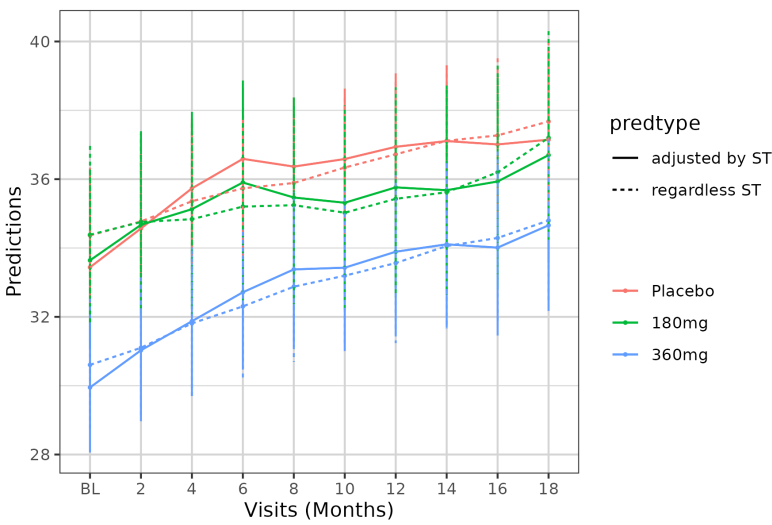


Figure 5 Pred. difference per month in total score by drug exposure against placebo

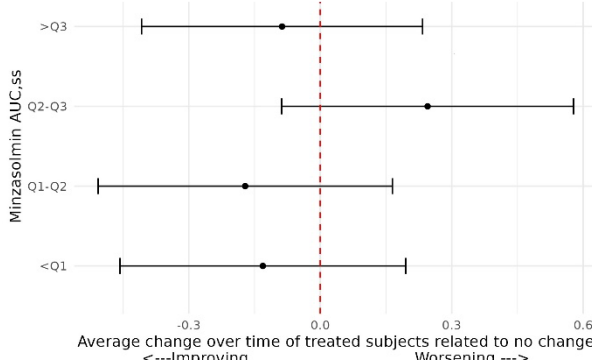


Table 1 Patient disposition and disease characteristics

	360 mg (180 mg bid) (N=159)	180 mg (90 mg bid) (N=160)	Placebo (N=156)
<i>Demographics</i>			
Age, years (mean[range])	59.8 [40;74]	61.4 [41;75]	61.2 [40;75]
BW, kg (mean[range])	79.2 [50;130]	76.8 [50;112]	75.3 [44;115]
Male, n (%)	94 (59.1) / 65 (40.9%)	99 (61.9) / 61 (38.1%)	94 (60.3) / 62 (39.7%)
Geo. region Europe/North America	117 (74%) / 42 (26%)	111 (69%) / 49 (31%)	105 (67%) / 51 (33%)
<i>Baseline disease characteristics (mean/median)</i>			
Total MDS-UPDRS score	31 / 28	34 / 31	34 / 34
Part III MDS-UPDRS score	20 / 19	22 / 19	23 / 20
Advanced disease severity (N)	1	7	2
<i>Miscellaneous</i>			
Discontinuation (%)	15	16	6
Start of ST (%)	55	55	60
Start of symptomatic treatment, months (mean/median)	11 / 12	11 / 12	11 / 10
Experienced worsening (%)	68	60	68

DaT-SPECT

- DaT-SPECT is a brain imaging technique used to evaluate the function of dopaminergic neurons in the brain.
- DaT-SPECT uses radiopharmaceutical tracers to bind to dopamine receptors and observe their distribution in the brain.

$$Y_{ij} = \alpha + BASE_i + \beta_1 * SEX_i + \beta_2 * AGE_{gr_i}^{(3)} + \beta_3 * Visit_{ij} + \gamma Visit_{ij} * TRT_i / PK_i^{(4)} + Error_{ij} \text{ for subject } i \text{ at time } j$$

Figure 6 Obs. change from baseline in function of drug exposure

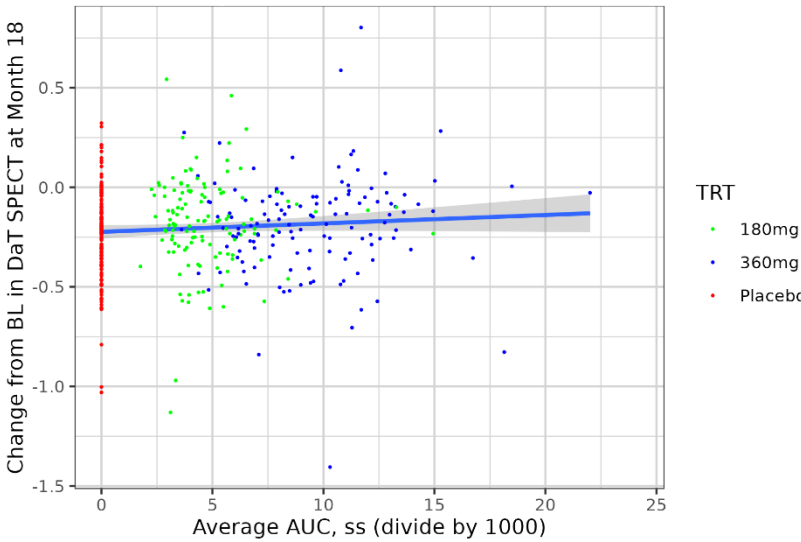
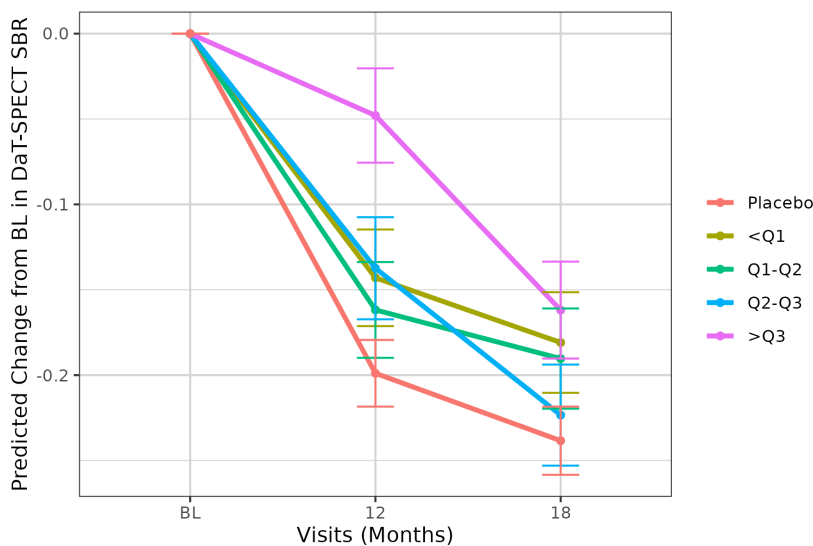


Figure 7 Pred. change from baseline by visit and quartiles of drug exposure



⁽¹⁾ ORCHESTRA study, NCT04658186AGE; ⁽²⁾ Carson S, et al. Results from ORCHESTRA, a phase II proof-of-concept study assessing the efficacy and safety of minzasolmin in people with early-stage

Parkinson's disease, oral presentation at AD/PD2025,Vienna, Austria ;

⁽³⁾ gr: Age groups, defined as [40-49], [50-59], [60-69] and [70+]; ⁽⁴⁾ PK: AUC at steady state, either as continuous or categorical based on its percentiles.

Bid: twice a day, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale, Obs.: Observed, PoC: Proof of concept, Pred.: Predicted, Q1 to Q3: quartiles of drug exposure, ST: symptomatic therapy, TRT: treatment

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