P8140 Final Project

Proposal for a Phase III trial: Prasinezumab in Patients with Parkinson's Disease

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1. Introduction and Background

Parkinson's disease (PD) is a common, long-term neurodegenerative disease, usually develops gradually and slowly, begins between ages of 55 and 65. Parkinson's disease affects dopaminergic neurons in the substantia nigra pars compacta, causing multiple motor and non-motor dysfunctions. Symptoms including tremors, muscle rigidity, difficulty in walking, talking and balance. About 1%-2% of the elder over 60 years old are suffering from Parkinson's disease.[1]

Pharmacologic treatments for Parkinson's disease include Levodopa, Nonergot dopamine agonists, Monoamine oxidase-B inhibitors and Catechol-O-methyltransferase inhibitors. Advanced therapies include deep brain stimulation, MRI-guided focused ultrasound.[2-3] However, those treatments are considered to target on alleviating motor system, not non-motor system. Some evidence even shows that dopaminergic medication can worsen the non-motor symptoms and lead to A.E.[4] To conclude, there is currently no standard of care for PD patients.

In our randomized, double-blind, two parallel group, placebo-controlled, superiority-design trial, we will investigate among patients with Parkinson's disease, is prasinezumab (IV 2000 mg every 4 weeks follow up 36 weeks) superior than placebo (IV 2000mg every 4 weeks follow up 36 weeks) in improving Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Total Score at week 36 comparing with baseline. Trail Population will be patients who are 40 years or older, diagnosed with

Parkinson’s disease according to International Parkinson and Movement Disorder Society (MDS) diagnostic criteria.[5]

2. Objectives

i. Primary

The primary outcome is the improvement of total Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) from baseline to week 36.

H0: The mean change of UPDRS in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) and placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up does not differ.

Ha1: The mean change of UPDRS in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is bigger than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

Ha2: The mean change of UPDRS in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is smaller than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

Our clinical interest is to discover if prasinezumab can improve mean UPDRS better than placebo (Ha1).

ii. Secondary

The secondary outcome are**(1)** change in Montreal Cognition Assessment (MoCA) Total Score, **(2)** time to worsening in motor or non-notor symptoms, **(3)** change in Schwab and England Activity of Daily Living (SE-ADL) Score.

(1) *H0:* The mean change of MoCA score in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) and placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up does not differ.

Ha1: The mean change of MoCA score in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is bigger than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

Ha2: The mean change of MoCA score in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is smaller than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

(2) *H0:* The probability of worsening in non-motor symptoms in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) and placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up does not differ.

Ha1: The probability of worsening in non-motor symptoms in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is larger than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

Ha2: The probability of worsening in non-motor symptoms in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is smaller than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

(3) *H0:* The mean change of SE-ADL score in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) and placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up does not differ.

Ha1: The mean change of SE-ADL score in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is bigger than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

Ha2: The mean change of SE-ADL score in patients with PD treating with prasinezumab (IV 2000mg every 4 weeks) is smaller than treating with placebo (IV 2000mg every 4 weeks) over 36 weeks individual follow-up.

iii. Safety

Three major safety outcomes will be focused during the trial.

(1) The proportion of participants showing serious AE like death, disabilities, etc. This outcome is assessed by clinicians and recorded as time-to-event data. SAEs will be monitored and reported continuously.

(2) The proportion of participants showing infusion-related reaction (IRR), like skin rash, tongue numbness, dysgeusia and pruritus.[6] This outcome is assessed by clinicians and

recorded as time-to-event variable. It'll be collected every time when participants received infusion.

(3) The proportion of participants showing all other treatment-emergent AEs like headache, nausea, diarrhea, dizziness and fatigue.[6] This outcome is assessed by clinicians and recorded as time-to-event variables. AEs will be monitored and reported continuously.

3. Trial Design

i. RCT feature

This is a double-blinded, randomized, placebo-controlled, superiority-design, Phase III trial with two parallel groups. At baseline, participants who meet the inclusion criteria will be independently allocated into Prasinezumab group and placebo group. Participants who are assigned with Prasinezumab will receive IV solution bag labeled as Prasinezumab with active Prasinezumab in it, and will get IV at 2000mg every 4 weeks, followed up 36 weeks. Participants who are assigned with placebo will receive IV solution bag labeled as Prasinezumab with placebo Prasinezumab in it, and will equally get IV at 2000mg every 4 weeks, followed up 36 weeks. During the trial, both participants and clinicians are unaware of what they're receiving.

All patients will be followed continuously and included in the ITT analysis, whatever their level of compliance. Every randomized patient will be analyzed in the group to which they were randomized at baseline, regardless whether they're compliant, whether they're killed, whether they withdrew consent, whether the outcome is missing.

ii. Blinding

All participants and health providers will be blinded during the trial, while the statisticians and accessors won't be blinded. To guarantee double-blinding, the trial will utilize centralized preparation of color-matched placebo treatments by using multivitamin solution. And the paraclinical examinations will be centralized assessed, unavailable to blinded participants and health care providers.

iii. Randomization

Stratified randomization with randomly permuted blocks will be used in this trial. Different block sizes with unequal proportions will be used, i.e. 60% size 4 blocks, 30% size 6 blocks and 10% size 8 blocks. The randomization will be stratified by site, since this is a multicenter clinical trial. Other variables, such as gender, race, etc, will not be stratified, due to balance will be achieved through overall randomization.

iv. Inclusion and Exclusion Criteria

Eligible participants have to be aged 40 years or older; Body weight range between: >/=45 kg/ 99 pounds (lbs) and less than or equal to (</=) 110 kg/242 lbs; Body mass index (BMI) of 18 to 34 kilograms per meter-squared (kg/m^2); Meet established diagnostic criteria for Parkinson's disease psychosis; Diagnosis of PD less than 3 years at screening; At Hoehn and Yahr Stage I or II; Currently not receiving levodopa, dopamine agonist or MAO-B inhibitors; Have psychotic symptoms developed after diagnosis and were present for at least 1 month.[7-8]

We exclude participants with: Known carriers of certain familial PD genes; Any significant cardiovascular condition; Any significant laboratory abnormality; Lactating women; Prior treatment with dopaminergic medication with no clinical treatment response; Participated in an investigational drug, device, surgical or stem cell study in PD.[7-8]

v. Enrolling Centers

In this trial, the type of enrolling centers will include major medical centers and hospitals.

vi. Data Coordination and Trial Management

The trial will be supported by Data Coordinating Center and Clinical Trial Management. DCC and CTM will provide statistical design and data analysis, coordinate and implement large multi-center RCTs.

vii. Sidedness of Test

Primary outcome will use a two-sided statistical test, since this is a superiority-design trial.

4. Data Collection and Patient Follow-up

i. Outcome Details

The primary outcome is the improvement of total Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) from baseline to week 36. It has been widely used in the clinical research and considered as one of the most accurate evaluation of Parkinson's disease. The total UPDRS is the sum of Part I, II, III and IV. Part I is non-motor experiences of daily living, with two components: IA are assessed by the research coordinator and IB is completed by the patient, independently of the research coordinator. Pat II is motor experiences of daily living and is reviewed by the investigator. Part III is motor examination; Part IV is motor complications and both Part III and IV are completed by research coordinator.[9] The UPDRS will be scored at baseline and after 36 weeks in enrolling centers, treated as continuous data and collected by data coordinator.

The first secondary outcome is the improvement of Montreal Cognition Assessment (MoCA) Total Score from baseline to week 36. MoCA test assesses several cognitive domains like short-term memory recall, visuospatial abilities working memory, etc.[10] It's a widely used assessment for detecting cognitive impairment and adopted in various clinical settings. It will be scored by research coordinator at baseline and after 36 weeks in enrolling centers, and recorded as a continuous variable by data coordinator.

The second secondary outcome is the probability of worsening in non-motor symptoms from baseline to week 36. Since the one of the purposes of prasinezumab is to treat non-motor symptoms occurring in PD patients, the logic of considering AE in symptoms as

secondary outcomes is reasonable. It will be collected by inquiries, assessed by clinicians and recorded as a time-to-event variable.

The third secondary outcome is the improvement of SE-ADL scale. SE-ADL is a widely used methods to evaluate patients' disability, it ranges from 0%(completely dependent) to 100%(completely independent), giving a indication of how well PD patients recover.[11] SE-ADL score will be assessed by clinicians at baseline and after 36 weeks, and recorded as a continuous variable by data coordinator.

ii. Data Collection Mechanism

The mechanism of data collection in this trial will be web-based data management system with Electronic Case Report Forms (eCRFs). It can meet the regulatory requirements of FDA, in addition, it can efficiently record and transmit large trial data among investigator, CRO and sponsor, comparing to faxed-based management system.

iii. Schedule of Visits

	SCREENING	RAND.	BASELINE (INFUSION 1)	INFUSION 2-9	EOT
Screening/Baseline:					
Study Informed Consent	X				
Medical history	X				
Medication history	X				
Inclusion and exclusion criteria	X				
Demographics	X				
Physical examination	X		X	X	X
Orthostatic vital signs	X		X	X	X
Randomization		X			
Primary outcome assessment:					
UPDRS			X		X
Secondary outcome assessment:					
MoCA			X		X
SE-ADL			X		X
Non-motor symptom inquiry			X	X	X
Safety Assessments:					
Infusion related reaction check			X	X	X
Adverse event inquiry			X	X	X

iv. Trial Timeline

5. Statistical Considerations

i. Type of Outcome

The primary outcome (MDS-UPDRS) will be recorded as a continuous variable, and analyzed with two-sided superiority Analysis of Covariance (ANCOVA) test, at 0.05 type I error.

ii. Power Calculation

The mean UPDRS for PD participants of control group in Phase II trial is 48.0.[6] According to previous studies, the average improvement of UPDRS in clinical trials is around 4.0 points over 36 months, with a standard deviation of 12.0 units.[12-13] So here we adopt the 4.0 points mean UPDRS difference as unadjusted effect size for primary outcome, i.e. μ_C=48.0, μ_I=44.0.

Since participants in both groups will receive infusion therapy under health workers' surveillance at enrolling centers, we expect the non-compliance and crossover to be minimal. Here we allow 2% crossovers, due to mislabeling or errors, 2% non-compliers and 96% compliers for both intervention group and placebo group. After calculation, we obtain an adjusted effect size of 3.76. (Appendix i.)

iii. Sample Size

We use PASS to calculate adjusted sample size with group-sequential tests. With 0.9 Power, 0.05 alpha, adjusted μ_C=47.88, μ_I=44.12, equal standard deviation of 12.0, we obtain the adjusted sample size: 219 for each group.

Group-Sequential Tests for Two Means (Legacy)

Numeric Results for Two-Sided Hypothesis Test of Means

Target Power	Actual Power	N1	N2	N	Mean1	Mean2	S1	S2	Alpha
0.90	0.90000	219	219	438	44.12	47.88	12.0	12.0	0.050

iv. Sensitivity Analysis

Total Sample Size with 0.9 Power

	δ=2.76	*δ=3.76	δ=4.76
σ =11.5	748	404	252
* σ =12.0	814	438	274
σ =12.5	884	476	298

Here is the sensitivity analysis with change in standard deviation and effect size. When standard deviation and effect size decrease, the total sample size will increase; when standard deviation and effect size increase, the total sample size will decrease.

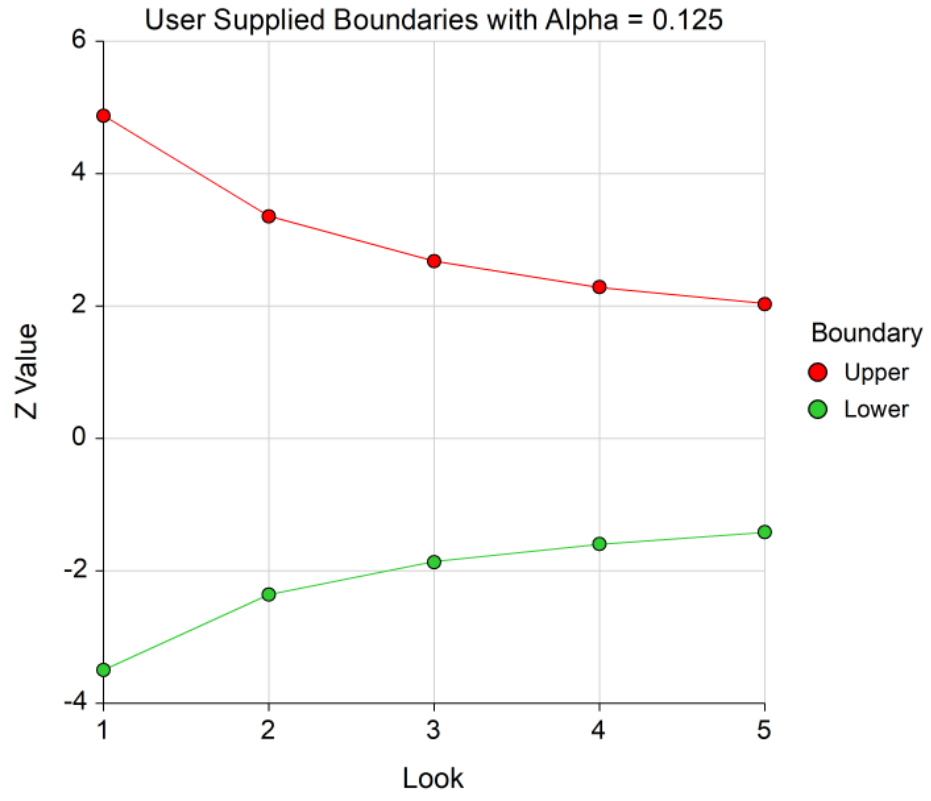
v. Interim Analysis

OBF Interim Analysis Boundaries

Details when Spending = User Supplied, N1 = 219, N2 =219, S1 = 12.0, S2 = 12.0, Diff = -3.76

Look	Time	Info	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.20	0	-3.49722	4.87688	0.000	0.000	0.000	0.00032	0.000
2	0.40	0	-2.35660	3.35695	0.010	0.009	0.010	0.09939	0.100
3	0.60	1	-1.86821	2.68026	0.035	0.028	0.038	0.34659	0.446
4	0.80	1	-1.59359	2.28979	0.067	0.041	0.078	0.29966	0.746
5	1.00	1	-1.41279	2.03100	0.100	0.047	0.125	0.15405	0.900

Drift 3.27879



This trial will include a pre-specified interim analysis using Group Sequential Methods, which will apply repeated significance test to accumulating data, thus controlling the type I error.

We use PASS(O'Brien-Fleming) to plan 5 interim analyses, with asymmetrical boundaries due to placebo control. When any associated z-score for the observed difference between the interventions lies outside the upper or lower boundary, the statistical terminal criteria achieved.

According to the results, in the first interim, when z-score of observed difference is larger than 4.9 or lower than -3.5, the trial reaches its statistical terminal criteria. In the last interim, the boundary shrinks to -1.4 to 2.0.

6. Safety Considerations

The first safety outcome is SAEs, which will be continuously monitored during the whole trial. Although previous study has proved that prasinezumab will not cause major serious adverse effects, we should still carefully treat it in case of the worst case.

The second safety outcome is IRR, which will be assessed by clinicians every time participants get infusion. IRR is a series of common adverse events during the intravenous infusion, however in extreme cases, IRR could affect and harm organs' normal functioning, even cause shock or death. In addition, IRR could be confounded with AEs induced by prasinezumab, and lead to biased assessment of interventions.

The third safety outcome is non-serious AEs, which will be measured by inquiry, and completed by participants. Collecting AEs data can help to better evaluate the safety issue of prasinezumab.

Other general safety issue, such as potential harm to neural system, cognition ability and mobility, will also be monitored during the trial.

7. Limitations and Late-breaking Problems

The major limitation of this trial is the measurements of all outcomes are through scaling or inquiry, which may not show same level of accuracy comparing to measurements conducting by medical devices or machine. Scaling results can be affected by clinicians and participants, and cause potential bias to the trial results.

The other limitation is the administration route of prasinezumab, which is by intravenous infusion. This is a less convenient and available methods comparing to oral tablets and oral solution, which leads to the problem that more loss-to-follow-up may occur during the trial.

Also, considering post-marketing situation, the infusion methods could cause much inconvenience to Parkinson's Disease patients, who have to go to the nearest medical centers or clinics every month to get medicated.

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Appendix i.

Calculation of Adjusted Effect Size

For intervention group:

μ_I=44.0, 2% crossovers, 2% non-compliers and 96% compliers

For control group:

μ_C=48.0, 2% crossovers, 2% non-compliers and 96% compliers

Adjusted mean UPDRS in intervention group is:

(0.02*48) + (0.02*46) + (0.96*44) = 44.12

Adjusted mean UPDRS in control group is:

(0.02*44) + (0.02*46) + (0.96*48) = 47.88

Adjusted Effect Size = 47.88 - 44.12 = 3.76