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Study ID: 2011-101-013

Title: A First-in-Human, Phase 1/2, Dose-ascending, Multicenter, Masked, Randomized, Vehicle-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AGN-241622 in Healthy Participants and Participants with Presbyopia (Stage 1 and Stage 2) and Efficacy in Participants with Presbyopia (Stage 2)

SAP Date: July 12, 2023

Statistical Analysis Plan for Study 2011-101-013

A First-in-Human, Phase 1/2, Dose-ascending, Multicenter, Masked, Randomized, Vehicle-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AGN-241622 in Healthy Subjects and Subjects with Presbyopia (Stage 1 and Stage 2) and Efficacy in Subjects with Presbyopia (Stage 2)

Date: 12 July 2023

Version 3.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for AGN-241622 Study 2011-101-013, A First-in-Human, Phase 1/2, Dose-ascending, Multicenter, Masked, Randomized, Vehicle-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of AGN-241622 in Healthy Subjects and Subjects with Presbyopia (Stage 1 and Stage 2) and Efficacy in Subjects with Presbyopia (Stage 2).

Due to Sponsor decision, the study was terminated after Stage 2a completion. This decision was not taken due to any safety reasons. The analysis described in this plan will be based on synoptic clinical study report (CSR).

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system. Pharmacokinetics analyses will be performed using Phoenix WinNonlin Version 8.3 or newer.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 12.1.

2.0 Study Objectives and Design

2.1 Study Objectives

The primary objective of this study is to evaluate the safety, tolerability, pharmacokinetics, and efficacy of AGN-241622 in healthy subjects and subjects with presbyopia.

2.2 Study Design Overview

Study 2011-101-013 is a Phase 1/2, multicenter, randomized, double-masked (except Cohort 7) study in healthy subjects and subjects with presbyopia. This study will be conducted in 3 stages (Stage 1, Stage 2a, and Stage 2b).

In Stage 1, the left eye will be the study eye and receive study treatment. In Stage 2a, both eyes will be study eyes and receive study treatment.

Study interventions by study stage and cohort are summarized in Table 1.

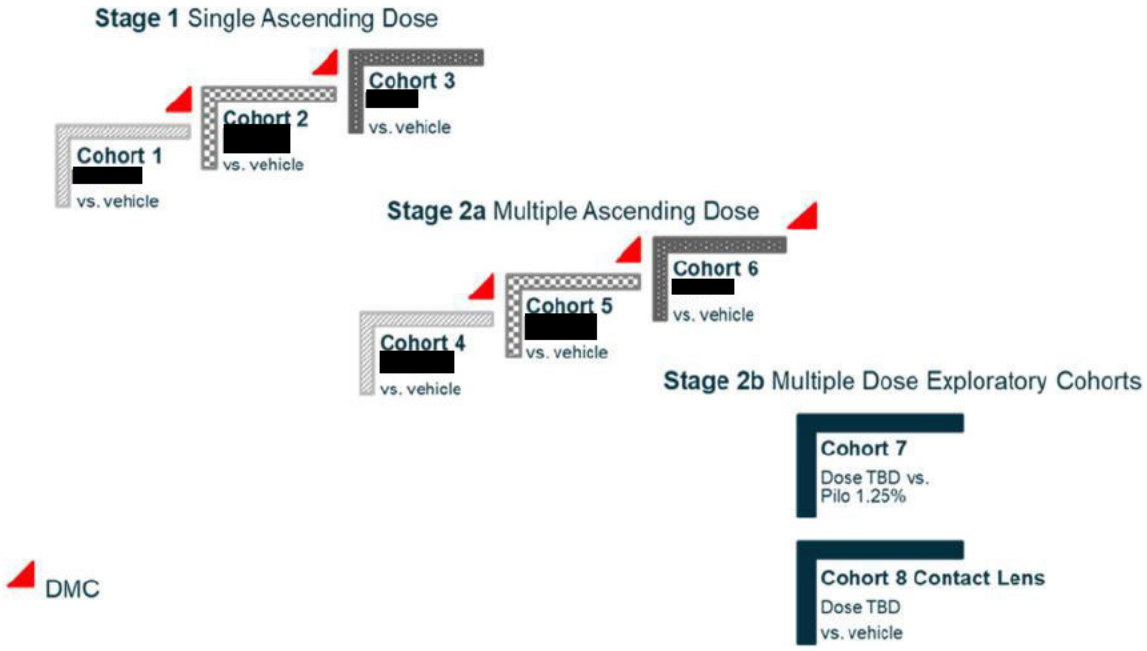
Table 1. Study Interventions by Study Stage and Cohort

Study Interventions by Study Stage and Cohort			
Stage 1	**Single Ascending Doses in Healthy Subjects**		
	Cohort 1	**Cohort 2**	**Cohort 3**
	AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle	AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle	AGN-241622 [redacted] single dose left eye 9 Active; 3 Vehicle
Stage 2a	**Multiple Ascending Dose in Subjects with Presbyopia**		
	Cohort 4	**Cohort 5**	**Cohort 6**
	AGN-241622 [redacted] Once daily (QD) x 14 days both eyes 9 Active; 3 Vehicle	AGN-241622 [redacted] QD x 14 days both eyes 9 Active; 3 Vehicle	AGN-241622 [redacted] QD x 14 days both eyes 9 Active; 3 Vehicle
Stage 2b*	**Multiple-Dose Exploratory Cohorts in Participants with Presbyopia**		
	Cohort 7	**Cohort 8**	
	AGN-241622 (dose strength to be determined [TBD]) versus pilocarpine HCl [redacted]) 1.25% QD x 14 days both eyes 60 (30 per treatment arm)	AGN-241622 (dose strength TBD) (in participants who wear contact lenses) QD x 14 days both eyes 9 Active; 3 Vehicle	

* Stage 2b has not been conducted due to early discontinuation of the study after completion of Cohort 6.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



The data monitoring committee (DMC) will review available unmasked safety and plasma pharmacokinetic (PK) data, along with target engagement and efficacy data if necessary (and applicable), from each completed cohort to recommend if it is acceptable to proceed to the next planned cohort, modify the proposed dose strength (e.g., de-escalate to a lower dose strength), repeat the current dose strength, modify the cohort size, or stop the study. In addition, the Food and Drug Administration (FDA) will review study data after the completion of each cohort and the sponsor will wait until a positive response is received from the FDA to proceed to the next cohort.

2.3 Treatment Assignment and Blinding

All subjects will be centrally assigned to study intervention using an interactive web response system (IWRS). In each cohort for Cohorts 1 to 6 and 8, approximately 12 participants will be randomized in a 3:1 ratio to receive AGN-241622 ophthalmic solution or vehicle. Cohorts 1 to 6 and 8 will be double-masked. In Cohort 7, 60 participants will be assigned in a 1:1 ratio to receive pilocarpine HCl ([redacted]) 1.25% ophthalmic solution or AGN-241622 ophthalmic solution. Cohort 7 will be single masked, in which participants will be masked for the study intervention assignment and site staff and the investigator will not discuss the study intervention assignment with the participants.

2.4 Sample Size Determination

The sample sizes for each study stage were not determined based on statistical consideration.

The sample sizes for each cohort are expected to provide sufficient data to assess safety, PK parameters (as applicable), and efficacy (as applicable) of each dose of AGN-241622.

3.0 Endpoints

Efficacy assessments are conducted in Stage 2 (Cohort 4, 5, 6, 7, and 8) only.

3.1 Primary Endpoint(s)

The primary efficacy endpoint is the proportion of subjects gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 14, Hour 3.

3.2 Other Efficacy Endpoint(s)

1. Proportion of participants gaining 2 lines or more in mesopic, high-contrast, binocular DCNVA
2. Change from baseline in mesopic, high-contrast, binocular DCNVA letters
3. Change from baseline in mesopic pupil diameter (mm) (distance and near)
4. Change from baseline in photopic pupil diameter (mm) (distance and near)
5. Change from baseline in photopic, high-contrast, binocular distance-corrected intermediate visual acuity (DCIVA) letters
6. Change from baseline in Near Vision Presbyopia Task-based Questionnaire (NVPTQ) (paper based) Performance score
7. Change from baseline in NVPTQ (paper based) Satisfaction score
8. Change from baseline in Presbyopia Impact and Coping Questionnaire (PICQ) Coping score

9. Change from baseline in PICQ Impact score

3.3 Safety Endpoint(s)

1. Adverse events (AEs)
2. Vital signs
3. 12-lead electrocardiogram (ECG)
4. Clinical laboratory assessments

3.4 Pharmacokinetic Endpoint(s)

Tear and plasma pharmacokinetic parameters.

3.5 Endpoint(s) to be analyzed for Synoptic CSR

Due to the early discontinuation of the Study after completion of Cohort 6, a synoptic CSR will be provided for this study, and only the endpoints 1 and 4 of Section 3.3 Safety Endpoints will be analyzed.

4.0 Analysis Population

The following population sets will be used for the analyses.

The intent-to-treat (ITT) population consists of all randomized subjects. The ITT population will be used for baseline analyses. Subjects will be included in the analysis according to the randomized study intervention.

The safety population consists of all subjects who received at least 1 administration of study intervention. Subjects will be summarized according to the study intervention they actually received.

For all analyses, vehicle groups will be pooled for Stage 1 and Stage 2a separately.

5.0 Subject Disposition

The number of subjects screened for the study will be provided.

The summary of study disposition post randomization will be provided in total and by study intervention for the following:

- Number of subjects randomized (this frequency count will be used as the denominator to calculate the percentages described below)
- Number and percentage of subjects treated
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who discontinued the study
- Reasons for discontinuation from the study

6.0 Study Treatment Duration

For Stage 2a, exposure to the study treatment will be summarized for treatment duration, calculated as the number of days from the date of the first dose of study intervention to the date of the last dose of study intervention, inclusive. Descriptive statistics will be presented.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Demographic parameters (age; age group (≤ 50, > 50); sex; race; ethnicity) will be summarized in total and by study intervention.

8.0 Safety Analyses

8.1 General Considerations

Safety data will be summarized for the safety population. Safety summaries will be presented by the treatment group for Stage 1 and 2a, respectively.

Vehicle groups will be pooled for Stage 1 and Stage 2a separately.

8.2 Adverse Events

8.2.1 Treatment-Emergent Adverse Events

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the first administration of study intervention.

A treatment-emergent serious adverse event (TESAE) is defined as a serious adverse event (SAE) that is also TEAE.

Ocular adverse events include those with locations noted by the investigator as OD or OS on the CRF.

8.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event by study intervention group for each cohort for below summaries. Additional summaries may be provided when applicable.

- TEAEs
  - Ocular
  - Nonocular
- Treatment-related TEAEs
  - Ocular
  - Nonocular

- Deaths
- TESAEs
  - Ocular
  - Nonocular
- Treatment-related TESAEs
  - Ocular
  - Nonocular
- TEAEs leading to discontinuation from study
  - Ocular
  - Nonocular

8.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, except for ocular AE, which is counted once for each eye.

- Ocular TEAEs by primary SOC and PT
- TEAEs by primary SOC, PT, and severity

8.2.4 Adverse Events Leading to Study Treatment Discontinuation

Listings of TEAEs leading to discontinuation will be presented.

8.3 Analysis of Laboratory Data

Descriptive statistics for values and changes from baseline in standard units at each assessment timepoint will be summarized.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Appendix B. The number and percentage of subjects who have at least one PCS postbaseline clinical

laboratory value will be tabulated. The denominator will be the number of subjects with available non-PCS baseline values and at least 1 postbaseline value. The numerator will be the number of subjects with available non-PCS baseline values and at least 1 PCS postbaseline value.

Subjects with PCS findings will be listed.

9.0 Pharmacokinetic Analyses

9.1 General Considerations

Descriptive statistics (arithmetic mean, standard deviation, relative standard deviation, maximum, median, minimum) will be reported for tear and plasma AGN-241622 concentration data at all timepoints by cohort, study intervention and study day.

Descriptive statistics (arithmetic mean, standard deviation, relative standard deviation, maximum, median, minimum) will be calculated for all PK parameters.

Analyses of plasma and tear PK will be performed for AGN-241622 treated subjects only. PK parameters will be calculated using standard Phoenix WinNonlin equations. AUC will be calculated by using the linear-log trapezoidal rule. In addition to the PK parameters listed in Section 9.2 and Section 9.3, additional parameters may be calculated, as necessary.

No formal statistical analysis of PK data will be performed.

9.2 Stage 1

Calculated plasma and tear PK parameters will include area under the concentration versus time curve from 0 to the last timepoint with measurable AGN-241622 concentrations (AUC_{0-t}), maximum observed concentration (C_{max}), and time to maximum observed concentration (T_{max}).

9.3 Stage 2a

Calculated PK parameters on Day 1 will include area under the concentration versus time curve from 0 to the end of the dosing interval ($AUC_{0\text{-}tau}$), maximum observed concentration (C_{max}), and time to maximum observed concentration (T_{max}).

Steady state PK parameters calculated on Day 14 will include $AUC_{0\text{-}tau,ss}$, $C_{max,ss}$, $T_{max,ss}$. Local and systemic accumulation will be assessed by calculating the accumulation index (AI) for AUC and C_{max} on Day 14.

Descriptive statistics will be used to summarize plasma trough concentrations on Days 2-7 and Day 14.

10.0 Interim Analyses

No interim analysis is planned.

10.1 Data Monitoring Committee

After Cohort 1, 2, 4, 5, and 6 are complete, an internal data monitoring committee (DMC) composed of individuals independent of 2011-101-013 study team at AbbVie and with relevant expertise in their field will review unmasked safety and plasma PK data, along with target engagement and efficacy data if necessary from the ongoing study, and will recommend if it is acceptable to proceed to the next planned cohort. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and general operations.

Since there are no efficacy analyses for early stopping, no alpha adjustment is needed.

11.0 Overall Type-I Error Control

Not applicable. No statistical testing is planned.

12.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	05 Nov 2020	Initial version
2.0	21 Jun 2023	Updated due to Sponsor early discontinuation of the study
3.0	12 July 2023	Updated due to the change for a synoptic CSR

12.1 Changes to Planned Analyses in the Protocol

Due to the early discontinuation of the study after completion of Cohort 6, there will not be any subjects in Stage 2b, hence no Stage 2b related analysis will be conducted. Changes from the originally planned statistical analysis specified in the protocol are outlined Table 3.

Table 3. Changes to Planned Analyses in the Protocol

Statistical Analysis Plan	Rationale for Changes
• No statistical analysis or outputs to be generated for Stage 2b or other objectives/endpoints • Synoptic CSR will be provided. Only key safety analysis will be performed.	Early study termination prior to Stage 2b

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]	Associate Director, Statistics	Author
[redacted]	Director, Statistics	Clinical Statistics
[redacted]	Senior Manager, Statistical Programing	Statistical Programming
[redacted]	Scientific Director	Medical/Scientific Monitor

Appendix B. Potentially Clinically Important Criteria for Safety

The potentially clinically significant criteria for clinical laboratory parameters are provided in the following section.

Table B-1 Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Parameter	SI Unit	Lower Limit	Higher Limit
CHEMISTRY			
Albumin	g/L	< 0.8 x LLN	> 1.2 x ULN
Alanine aminotransferase	U/L		≥ 3.0 x ULN
Alkaline phosphatase	U/L		≥ 3.0 x ULN
Aspartate aminotransferase	U/L		≥ 3.0 x ULN
Bicarbonate	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Bilirubin, total	µmol/L		≥ 1.5 x ULN
Blood urea nitrogen	mmol/L		> 1.5 x ULN
Calcium	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Chloride	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Cholesterol, total	mmol/L		> 1.6 x ULN
Creatinine	µmol/L		> 1.5 x ULN
Creatine kinase	U/L		> 2.0 x ULN
Estimated glomerular filtration rate	mL/min/1.73 m^2	< 0.8 x LLN	
Glucose, fasting	mmol/L	< 0.8 x LLN	> 2.0 x ULN
Phosphorus	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Potassium	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Protein, total	g/L	< 0.9 x LLN	> 1.1 x ULN
Sodium	mmol/L	< 0.9 x LLN	> 1.1 x ULN
Triglycerides	mmol/L		> 2.0 x ULN
Uric acid	µmol/L		> 1.2 x ULN
HEMATOLOGY			
Basophils, absolute cell count	10^9/L		> 2.0 x ULN

Parameter	SI Unit	Lower Limit	Higher Limit
Eosinophils, absolute cell count	10^9/L		> 2.0 x ULN
Hematocrit	Ratio	< 0.9 x LLN	> 1.1 x ULN
Hemoglobin	g/L	< 0.9 x LLN	> 1.1 x ULN
Lymphocytes, absolute cell count	10^9/L	< 0.7 x LLN	> 1.3 x ULN
Parameter	SI Unit	Lower Limit	Higher Limit
Monocytes, absolute cell count	10^9/L	< 0.5 x LLN	> 2.0 x ULN
Neutrophils, absolute cell count	10^9/L	< 0.7 x LLN	> 1.3 x ULN
Platelet count	10^9/L	< 0.5 x LLN	> 1.5 x ULN
Red blood cell count	10^{12}/L	< 0.9 x LLN	> 1.1 x ULN
White blood cell count	10^9/L	< 0.9 x LLN	> 1.5 x ULN
URINALYSIS			
pH	pH	< 0.9 x LLN	> 1.1 x ULN
Glucose	-		Positive[a]
Protein	-		Positive[b]
Specific gravity			> 1.1 x ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory; SI = Le Système International d'Unités (International System of Units)

a. Any results other than negative will be considered as positive.

b. Any results other than trace or negative will be considered as positive.