Study Title: A Phase III Randomised, Placebo-controlled, Double-blind, Multi-centre, Clinical Trial to Determine the Efficacy and Safety of Presendin in Idiopathic Intracranial Hypertension

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Statistical Analysis Plan: Abbreviated Final Analysis, Final Version 1.0, dated 02-Nov-2023

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Document History

Version	Date	Change(s)	Author
Final Version 1.0	02NOV2023	Initial final version	Karola Köhler

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
eCRF	electronic case report form
CSR	clinical study report
DSMC	data safety monitoring committee
IIH	idiopathic intracranial hypertension
MedDRA	medical dictionary for regulatory activities
PT	preferred term
SAE	serious adverse event
SAF	Safety population
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

1. Overview

This statistical analysis plan (SAP) describes the planned abbreviated analysis and reporting for Invex Therapeutics protocol number INVEX-CLIN-IIH-301 (A Phase III randomised, placebo-controlled, double-blind, multi-centre, clinical trial to determine the efficacy and safety of Presendin™ in idiopathic intracranial hypertension), protocol version 4.0, dated 09JUL2022, and protocol version 5.0 (countries of the European Union), dated 08DEC2022.

The study was early terminated due to commercial reasons in Aug 2023, with only a very small number of patients enrolled. All patients finally consented were in countries working with protocol version 4.0.

This analysis plan only covers the analysis that is finally planned to be conducted for this early terminated study.

The statistical plan described hereafter is an *a priori* plan. It will be approved before any unblinded inferential or descriptive analysis of data pertaining to Invex Therapeutics's study INVEX-CLIN-IIH-301.

2. Study Objectives and Endpoints

Original study objectives and endpoints are listed in protocol section 2. It was decided to restrict the planned analysis to the most relevant safety endpoints only (adverse events and safety laboratory data).

3. Overall Study Design and Plan

3.1. Overall Design

This is a randomised, placebo-controlled, double-blind, multi-centre clinical trial, initially planned in approximately 240 randomised patients with idiopathic intracranial hypertension (IIH).

The trial is designed as follows:

The trial begins with a 1-week screening period. The screening period is followed by a 24-week randomised double-blind treatment period in which patients will be randomised (1:1) to receive a subcutaneous (SC) dose of either Presendin containing 2mg of exenatide (active group) or matching placebo (placebo group), self-administered once weekly. At the end of the randomised treatment period (Week 24), all patients have an end of treatment clinic visit. Five weeks after the end of that treatment visit, an end of trial safety follow-up telephone visit is performed. For full details of the study design, please see the protocol.

3.2. Study Population

Patients with a diagnosis of IIH according to the protocol and meeting the eligibility criteria.

3.3. Treatments Administered

There are two treatment groups with patients randomised in a ratio of 1:1 to receive active treatment (Presendin) or placebo.

3.4. Schedule of Events

Please see protocol Table 1 for a detailed schedule of study assessments.

4. Statistical Analysis and Reporting

The final statistical analysis will be performed after the clinical study database is locked and the study is unblinded. A synoptic clinical study report (CSR) summarizing all planned analyses according to this analysis plan will be prepared. Other analyses as part of the protocol are finally not planned to be performed by statistics due to the early study termination. In addition, the medical writer may review relevant raw data and relevant conclusions based on raw data may be included in the CSR.

4.1. Introduction

Data processing and tabulation of descriptive statistics will primarily use SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of patients in the relevant analysis population for the treatment groups, unless otherwise specified. The denominator for by-visit displays will be the number of patients in the relevant analysis population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Due to the early study termination all statistical analyses performed will be descriptive.

4.2. Interim Analysis and Data Monitoring

A Data Safety Monitoring Committee (DSMC) was planned to be established for this study.

Finally due to early study termination, no DSMC meeting other than the DSMC kick-off meeting took place; thus, no unblinded data were presented to the DSMC.

Also, no other formal interim analyses were planned or conducted.

5. Analysis Populations

Due to the early termination of the study, all tables and listings (except disposition information) are planned to be presented for the Safety population. No other analysis populations will be implemented.

Safety Population (SAF): The Safety population includes all patients randomised to treatment (active or placebo) who received at least one dose of study medication.

Due to the limited number of patients, it is likely that the unblinded randomized treatment will match the actual treatment in all cases. This will be re-checked based on the unblinded data. If there are no discrepancies, a footnote will be added to the output to indicate that actual and randomized treatment are the same for all patients. If any discrepancies occur between randomized and actual treatment, the actual treatment will be used for all tables/listings. Any patient who received Presendin at least once will be included under Presendin treatment for all tables/listings. In this case, the information about the randomized treatment will be added to the diposition listing.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

There is no specific baseline definition. Tables by visit will contain “Screening (Visit 1) – Week – 1” as well as “Baseline (Visit 2) – Week 0 (Day 1)” reported separately. Changes from baseline will not be calculated.

6.1.2. Analysis Visits

In general, scheduled visits as reported in eCRF will be used for analysis. No visit windowing is planned.

7. Study Patients and Demographics

7.1. Disposition of Patients and Withdrawals

Disposition of patients will include tabulations of the number of screened patients, tabulated reasons for screen failure, number of patients randomised into each treatment group, the number of patients who received treatment, the number of patients completing 24-weeks of randomised treatment, the number of patients completing study, tabulated reasons for discontinuation from the

study, tabulated reasons for discontinuation of study medication (without withdrawal from study) and number of patients in the Safety population.

In addition, treatment and study completion status and reasons for study withdrawals will be listed.

7.2. Demographics and Other Baseline Characteristics

Summary statistics for age, sex, race, and ethnicity will be presented by treatment group and overall.

All demographic and baseline characteristics will also be displayed in a data listing.

7.3. Exposure and Compliance

Investigational product administration will be listed based on the exposure (study drug administration) page from the eCRF.

8. Safety and Tolerability Analysis

Safety will be evaluated from reported adverse events (AEs) and clinical laboratory values.

All safety analyses will be performed on the Safety population.

8.1. Adverse Events

All AEs, treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 25.0 or later).

An AE is defined as treatment-emergent if the first onset or worsening is after the first administration of study medication.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst-case approach).

For missing or partial AEs onset dates and times, the convention for replacing missing or partial dates will be the following based on the worst-case approach:

For partial AE start dates:

- If the year is unknown, then do not impute the date but assign a missing value. The AE will then be considered as a TEAE.
- If the month and day are unknown, then:
    - If the year matches the year of first treatment date, and the end date (if present) is after first treatment date, then impute as the month and day of the first treatment date.
    - Otherwise, assign 1st of January.

- If only the day is unknown, then:
  - If the month and year match the month and year of the first treatment date, then impute as the day of first treatment date.
  - If this produces a date after the AE end date, assign the start date to the 1st day of the month.
  - Otherwise, assign the 1st day of the month.

Missing or partial AE end dates will not be replaced.

If partial or missing times occur for AE at the day of first treatment, AE will be considered as TEAE, unless it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst-case approach).

An overall summary table of TEAEs will be produced.

The number and percentage of patients reporting TEAEs, grouped by MedDRA system organ class (SOC) and preferred term (PT), will be tabulated by treatment group. Summaries will be presented for all TEAEs and treatment-related TEAEs.

In the case of multiple occurrences of the same TEAE within the same patient, each patient will only be counted once for each PT.

If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = Grade 4/life-threatening, relationship = probable relationship).

In the AE data listings, all AEs will be displayed. Adverse events that are treatment-emergent will be indicated as such.

8.2. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages of patients) of TEAEs leading to withdrawal of study drug and/or study discontinuation by treatment group, SOC, and PT will be tabulated.

8.3. Serious Adverse Events

A summary of incidence rates (frequencies and percentages of patients) of SAEs by treatment group, SOC, and PT will be tabulated.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the eCRF.

8.4. Adverse Events of Special Interest

No adverse events of special interest are defined in the protocol.

8.5. Clinical Laboratory Evaluations

Laboratory test results for each biochemistry (including glucose) and haemotology parameters (including coagulation) will be summarized descriptively by treatment group and timepoint as observed values.

The number of patients with clinical laboratory (biochemistry and haemotology) values categorized as below, within, or above the normal ranges will be tabulated in a frequency table for each clinical laboratory analyte by treatment group and timepoint.

Abnormal laboratory values will be displayed in the data listings, along with corresponding normal ranges.

9. Changes from Planned Analysis

As the study is early terminated, only an abbreviated analysis will be conducted. Thus, not all analyses from the protocol will finally be conducted.

10. Other Planned Analysis

No other analyses are planned for this study.

11. Tables and Listings

11.1. Planned Table and Listing Shells

Table of contents of planned tables and listings together with table and listing shells will be presented in a separate document.