SYNOPTIC CLINICAL STUDY REPORT

A Phase III randomised, placebo-controlled, double-blind, multi-centre, clinical trial to determine the efficacy and safety of Presendin in idiopathic intracranial hypertension

1 TITLE PAGE

Protocol Number:	INVEX-CLIN-IIH-301
Study Phase:	Phase III
First Participant Enrolled:	18-Nov-2022
Last Participant Completed:	18-Sep-2023
Study Completed:	20-Oct-2023
Sponsor's Responsible Medical Person:	Carol Parish Chief Operating Officer Invex Therapeutics Ltd.
Sponsor:	Invex Therapeutics Ltd.
Document Date:	Final v1.0; 05-Dec-2023
This study was conducted in accordance with the International Council on Harmonisation (ICH), Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complies with the obligations and requirements of the Clinical Investigator and other requirements as listed in Title 21 of the United States Code of Federal Regulations (CFR) and other applicable regulations	

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Title of Study: A Phase III randomised, placebo-controlled, double-blind, multi-centre, clinical trial to determine the efficacy and safety of Presendin in idiopathic intracranial hypertension

Investigators: The following investigators enrolled participants:

Celia Chen MD, Anneke Van Der Walt MD, Helen Danesh-Meyer MD, Susan Mollan MD, Rosa Tang, MD.

Refer to Appendix 16.1.3 for a full listing of all initiated sites. See Appendix 16.1.4 for full details of investigators.

Study Centre(s): This was a multi-centre study with an expected 40 centres, of which 16 were activated. A total of 27 patients was screened, out of which 14 participants were randomised at 5 centres. Another 2 centres saw screen failure patients only.

Publication (reference): None

Protocol: the protocol and all amended versions are presented in Appendix 16.1.1.

Original version 1.0 02-Dec-2021

Version 2.0 17-Mar-2022

Version 3.0 08-Jun-2022

Version 4.0 09-Jul-2022 – all participants were enrolled under this version

Version 5.0 (EU only) 08-Dec-2022

Date of First Enrollment: 18-Nov-2022 **Date of Last Participant Visit:** 18-Sep-2023 **Date of Study Termination**: 21-Aug-2023 **Date of Study Completion**: 20-Oct-2023 **Database Lock:** 14-Nov-2023	**Phase of Development**: Phase III

OBJECTIVES:

The primary objective of this study was as follows:

- To determine the efficacy of Presendin administered subcutaneously (SC) once weekly for 24 weeks to participants with idiopathic intracranial hypertension (IIH), as determined by change in intracranial pressure (ICP), as measured by lumbar puncture (LP) at baseline and at 24 weeks.

The secondary objectives of this study were to determine the effect of Presendin on change in the following:

- Perimetric mean deviation (PMD) as measured by the Humphrey Visual Field analyser (24-2 Swedish Interactive Testing Algorithm-Standard)

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- Papilloedema as measured by optical coherence tomography imaging (retinal nerve fibre layer thickness and optic nerve head volume measurements)
- Monthly headache days (MHD)
- Moderate to severe MHD
- Headache responder rate (≥50% reduction in MHD)
- Headache responder rate (≥50% reduction in moderate to severe MHD)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

Safety Objective:

The objective was to determine the safety of Presendin administered SC once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG), and routine laboratory assessments.

METHODOLOGY:

This was a randomised, placebo-controlled, double-blind, multi-centre study requiring 240 adult randomised participants with IIH to determine the efficacy and safety of Presendin. Exenatide pharmacokinetics (PK) were to be conducted and and provision was made to conduct population PK modelling, if applicable.

Consenting participants with a diagnosis of IIH entered a 1-week screening period, in which there was no investigational product (IP) treatment, to gather baseline measurements and to check eligibility. Although a headache diary is typically over 28 days, it was considered unethical to have participants off treatment for this more prolonged period due to the real risk of visual loss. Hence, the baseline headache frequency was calculated over 1 week as has been done in other studies.[1,2,3] Figure 1 displays the study schema.

[1] Wall M, McDermott MP, Kieburtz KD et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA.* 2014 Apr 23-30;311(16):1641-51.

[2] Markey KA, Ottridge R, Mitchell JL et al. Assessing the Efficacy and Safety of an 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor (AZD4017) in the Idiopathic Intracranial Hypertension Drug Trial, IIH:DT: Clinical Methods and Design for a Phase II Randomized Controlled Trial. *JMIR Res Protoc.* 2017 Sep 18;6(9):e181.

[3] Mollan S, Wakerley B, Alimajstorovic Z, et al. Intracranial Pressure Directly Predicts Headache Morbidity in Idiopathic Intracranial Hypertension. *J Headache Pain.* 2021 Oct 7;22(1):118.

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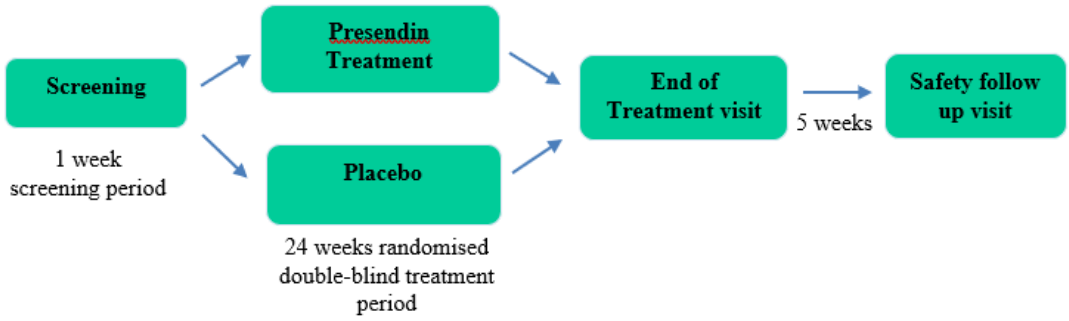
At the screening visit, participants were provided with training on the self-administration of the IP and were provided with a leaflet to take home. Participants were asked to self-administer 1 dose of placebo during the screening visit to ensure they were comfortable with self-injection. Participants who were not comfortable with self-administration were deemed a screen failure and were not randomised into the study. Eligible participants were then randomised to receive either Presendin or matching placebo for 24 weeks in a 1:1 ratio. After completing the randomisation period participants had an end of treatment clinic visit. Five weeks after the end of treatment visit, an end of study safety follow-up telephone visit was also performed.

Figure 1: Study Schema



NUMBER OF PARTICIPANTS (PLANNED AND ANALYSED): It was anticipated that 240 participants would be enrolled at 40 investigative centres participating in the study (120 participants in each treatment arm). The actual number of participants enrolled at the time the study was early terminated on 21-Aug-2023 was 14 participants at 5 investigative centres.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Study Indication: idiopathic intracranial hypertension

Participants over 18 years old, able to provide written informed consent and who had a diagnosis of new IIH by consensus criteria (see Appendix 16.1.1, Protocol Section 17.2, Appendix 2), including normal structural brain imaging (excluding features of raised ICP and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary cause of raised ICP. Participants must have had LP opening pressure ≥25 cm cerebrospinal fluid (CSF) at diagnosis. Participants must also have had bilateral papilloedema (Frisén grade ≥1) verified by the optical coherence tomography Reading Centre, and PMD defined as between -2 to -7 decibels in at least 1 eye. Eyes meeting this criterion were defined as 'study eyes.' Reproducible visual loss must have been present on automated perimetry including no more than 15% false positive responses (reliability confirmed by the Visual Field Reading Centre) in study eyes.

In addition, participants must have had 2 or more headache days over the 7-day period prior to screening and during the 7-day screening period.

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Participants must have been of non-childbearing potential or, if of childbearing potential, must have had a negative pregnancy test and must have agreed to use a highly effective birth control method (see Appendix 16.1.1, Protocol Section 17.8, Appendix 8 for further details) during the whole study duration including the last follow-up visit (12 weeks after ceasing drug). Lactating participants must have agreed to stop breast-feeding. Male participants with a partner of childbearing potential must have committed to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the study, including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they were of childbearing potential, must have agreed to practice contraception and to use a highly effective method of contraception during the study, including the last follow-up visit (12 weeks after ceasing IP).

Potential participants were excluded if they had presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography. Those who had previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression were also excluded, as were those with previous bariatric surgery within the last 3 months or intention during the study.

Abnormal neurological examination (aside from papilloedema and consequent visual loss or 6^{th} or 7^{th} nerve palsy or palsies), treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate [including if used as a migraine preventative], diuretics, glucocorticoids [intravenous, injectable steroids or oral (including dexamethasone and prednisolone)]); nasal, inhaled, or topical steroids were allowed, or use of any drugs known to cause intracranial hypertension, including exposure to fluoroquinolones, lithium, vitamin A, or tetracyclines within 2 months prior to diagnostic LP were all exclusionary.

In addition, potential participants with any disease other than refractive error that caused visual loss in the study eyes were excluded. Where there was uncertainty this would be determined by the Independent Adjudication Committee (IAC). Potential participants who had refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in the study eyes were also excluded. In addition, potential participants with myopia of worse than -6.00 D sphere but ≤ -8.00 D sphere were eligible if they wore a contact lens for all perimetry examinations with the appropriate correction. Participants must have been able to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes; where there was uncertainty this would be evaluated by the IAC.

Other exclusion criteria such as medical history, concomitant illness/conditions, contraindications to IP or procedures, and laboratory analyte thresholds are described in Appendix 16.1.1, Protocol Section 5.2.2.

A participant would also be excluded if they did not complete ≥6 days of electronic/paper study diary during the 7-day screening period, or if they were unable to self-administer the IP (or unable to administer IP with support) after receiving training during the screening period.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Presendin (2.0 mg exenatide) was self-administered as an SC injection, once weekly. Presendin was supplied as 2 parts, 1 vial consisting of a drug part (white or greyish white powder in a clear vial) and 1 pre-filled syringe containing the diluent part (colourless liquid). The drug part was suspended in the diluent part solution and administered as a suspension.

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Test product lot numbers: EX21004A.US; EX222001; EX21004A

DURATION OF TREATMENT:

The duration of the study for each participant was to be up to 30 weeks, which included a 1-week screening period, a 24-week randomised double-blind treatment period, and a 5-week treatment follow-up period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:
Placebo was self-administered as an SC injection, once weekly. Placebo was supplied as 2 parts (visually identical to the Presendin vial and pre-filled diluent syringe). The drug part excluded the active pharmaceutical ingredient (exenatide acetate) and the diluent part was the same as the active treatment diluent. The drug part is suspended in the diluent part solution and administered as a suspension.

Placebo lot numbers: INVEX-CLIN-IIH-301.PL; INVEX-CLIN-IIH-301.M.PL; INVEX-CLIN-IIH-301.N.PL; INVEX-CLIN-IIH-301.X.PL; INVEX-CLIN-IIH-301.Y.PL; IIH-301-1; EP222002; EX21003A.US; IIH-301-2; IIH-301-3; IIH-301-4; IIH-301-5; IIH-301-6.GL; IIH-301-6.US

CRITERIA FOR EVALUATION:

Primary Endpoint

Efficacy:

The primary endpoint was the change in ICP from baseline to Week 24 measured by LP.

Secondary Endpoints

- Perimetric mean deviation
- Retinal nerve fibre layer thickness
- Optic nerve head size
- The number of MHD
    - Monthly headache days included all headache days, defined as those with an onset, continuation or recurrence, any severity or phenotype of headache, and lasting at least 30 minutes or which required acute headache analgesia.
- Number of monthly moderate to severe headache days.
    - A moderate/severe headache day was defined as a day with moderate or severe pain that lasted at least 4 hours or that required acute headache analgesic medications.
- Responder rate MHD (defined as a ≥50% reduction)
- Responder rate moderate to severe MHD (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point numeric rating scale, 0-10 where 0 = no pain and 10 = most severe pain)
- Use of acute headache analgesic medications (acute headache analgesics in days per month)
- Visual acuity as measured by logarithm of the minimum angle or resolution (LogMAR) units

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- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP

Safety Endpoints:

- Vital signs
- Adverse events: treatment-emergent adverse events (TEAEs), serious adverse events (SAEs)
- Resting 12-lead ECG
- Routine laboratory assessments (haematology, coagulation, and biochemistry)

STATISTICAL METHODS:

The study was terminated early due to commercial reasons on 21-Aug-2023, with 14 participants enrolled. The planned analyses in the protocol were not conducted; instead, the planned analyses were restricted to the most relevant safety endpoints only (AEs and safety laboratory data) per the statistical analysis plan version 1.0, dated 02-Nov-2023. In addition, relevant raw data were reviewed to arrive at relevant conclusions in the clinical study report. Due to the early study termination all statistical analyses performed are descriptive.

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

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

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

The Safety population includes all participants randomised to treatment (active or placebo) who received at least 1 dose of IP.

Summary statistics for age, sex, race, and ethnicity are presented by treatment group and overall. All demographic and baseline characteristics are also displayed in a data listing.

Investigational product administration is listed based on the exposure (IP administration) page from the electronic case report form (eCRF).

Safety is evaluated from reported AEs and clinical laboratory values.

All AEs, TEAEs, and SAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 25.0). Summaries of incidence rates (frequencies and percentages of participants) of TEAEs leading to withdrawal from the study and SAEs by treatment group, system organ class, and preferred term, are tabulated. A data listing of SAEs is also provided, displaying details of the event(s) captured on the eCRF.

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

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

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

SUMMARY – CONCLUSIONS:

The sponsor terminated the study prematurely. At the time of termination, 14 participants had been treated. No PK samples were analyzed. A limited analysis was conducted on the most relevant safety data and results are presented herein.

Participant Disposition: Out of 27 screened, 14 participants were randomized: 8 to Presendin and 6 to placebo. Four participants (28.6%) completed treatment: 3 (37.5%) in the Presendin group and 1 (16.7%) in the placebo group. One participant (12.5%) in the Presendin group discontinued treatment due to an AE. The remaining 9 participants (64.3%) discontinued treatment at the sponsor's request/due to study termination (Table 14.1.1; Listing 16.2.1). Patients who prematurely discontinued treatment and/or study due to early study termination are displayed under reason "sponsor request" or "other," depending on the site entry.

Mean (SD) age of the 14 randomized participants was 28.2 (7.06) years, ranging from 18 to 39 years. The majority (13 participants, 92.9%) were female; of the 14 participants, 10 (71.4%) were White and 13 (92.9%) were not Hispanic or Latino. Demographics were similar between treatment groups (Table 14.1.2; Listing 16.2.4).

Investigational Product Dosing: Treatment exposure is presented in Listing 16.2.5.

Safety Results

Treatment-emergent Adverse Events: An overview of TEAEs is provided in Table 14.3.1.1; all AEs are listed in Listing 16.2.7.1. Overall, all 14 participants experienced at least 1 TEAE during their study participation. Nine participants (64.3%) experienced a TEAE considered related to IP: 5 participants (62.5%) in the Presendin group and 4 participants (66.7%) in the placebo group. There were no deaths and no SAEs reported. One participant (12.5%) in the Presendin group had a severe TEAE that led to discontinuation (injection site indentation). A narrative for this participant is presented in Section 14.3.1.

Treatment-emergent AEs occurred most frequently in the General disorders and administration site conditions system organ class (SOC) (8 participants [57.1%]). Five participants (62.5%) in the Presendin group and 3 participants (50.0%) in the placebo group experienced TEAEs in this SOC. The most common TEAEs were administration site conditions, which occurred in 5 participants (62.5%) in the Presendin group compared with 1 participant (16.7%) in the placebo group. The most commonly reported preferred term in this SOC was injection site mass, reported by a total of 3 participants (21.4%); 2 (25.0%) in the Presendin group and 1 (16.7%) in the placebo group (Table 14.3.1.2). Injection site mass was considered related to treatment in both participants in the Presendin group (Table 14.3.1.3). The following administration site conditions in the Presendin group were also considered related to treatment and occurred in 1 participant (12.5%) each: injection site hypersensitivity; injection site indentation; injection site pain; injection site pruritus; and injection site swelling. One participant (16.7%) in the placebo group had a treatment-related TEAE of injection site rash.

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Six participants (42.9%) reported TEAEs in the Infection and infestation SOC; all were in the Presendin group. Three participants (37.5%) had COVID-19 infections (Table 14.3.1.2). None of the infections/infestations TEAEs was considered related to treatment (Table 14.3.1.3).

Gastrointestinal (GI) disorders were reported in 5 participants (35.7%): 2 (25.0%) in the Presendin group and 3 (50.0%) in the placebo group. The most common GI TEAE was diarrhoea, reported in 2 participants (33.3%) in the placebo group; both were considered related to treatment. One participant (12.5%) in the Presendin group had a treatment-related GI TEAE of abdominal discomfort.

The following TEAEs were also considered related to treatment and were reported in 1 participant each: hypoglycaemia in the Presendin group; and visual impairment; blood pressure systolic increased; and headache in the placebo group.

Safety Laboratory Data: The majority of participants in both treatment groups had normal laboratory values at all visits (Table 14.3.4.1; Listing 16.2.8). Abnormalities that were present at Baseline occurred at other visits during the study with similar incidence between the treatment groups, with no evident pattern over time. Observed values for laboratory data are presented in Table 14.3.4.2; there were no important mean changes over time. By-participant laboratory data are presenting in Listing 16.2.8.

Other Safety Data: A review of ECG and vital signs data indicated no clinically significant abnormal changes over time.

CONCLUSION:

Due to the limited number of participants enrolled in the study at the time of study termination, no conclusions regarding safety can be made, although available data indicate the treatment was well tolerated. The most common TEAEs considered related to IP were administration site conditions, which occurred in 5 participants (62.5%) in the Presendin group compared with 1 participant (16.7%) in the placebo group. One participant in the Presendin group had a severe injection site mass that led to discontinuation.

Due to a commercial re-evaluation of the program by the sponsor, the study was terminated prematurely i.e., early terminated (21-Aug-2023). The reason for early termination was not for efficacy and/or safety reason(s). There were no reported SAEs in this study. Efficacy was not analyzed at all.

DATE OF THE REPORT: 05-Dec-2023

14 TABLES

14.1 Demographic Data

Table 14.1.1 Summary of Subject Disposition (All Subjects)

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Table 14.3.1.2 Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.3 Treatment Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.4 Treatment-emergent Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term (Safety Population)

Table 14.3.2 Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

Table 14.3.4.1 Laboratory Abnormalities – Chemistry, Hematology, Coagulation (Safety Population)

Table 14.3.4.2 Laboratory Data – Observed Values – Chemistry, Hematology, Coagulation (Safety Population)

14.3.1 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Clinically Meaningful Adverse Events

- Participant 840002-003

16 APPENDICES

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16.1.4 List and Description of Investigators and Other Important Participants in the Study

16.1.5 Signature of Sponsor's Responsible Medical Officer

16.1.6 List of Study Intervention Lot Numbers (not applicable)

16.1.7 Randomisation Scheme and Codes

16.1.8 Audit Certificates (not applicable)

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16.1.11 Publications Based on the Study (not applicable)

16.1.12 Important Publications Referenced in the Report

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Listing Number	Listing Title
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16.2.6 Protocol Deviations

16.3 Case Report Forms

16.3.1 Case Report Forms for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.3.2 Other Case Report Forms Submitted (not applicable)

16.4 Individual Participant Data Listings (US Archival Listings) (not applicable)