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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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
Effective Date:	08Dec2022
EudraCT #	2021-006664-24

Short Title: A Phase III trial to determine the efficacy and safety of Presendin in IIH – IIH EVOLVE

Abstract: Idiopathic intracranial hypertension (IIH) has significant associated morbidity and reduced quality of life. There is a significant risk of visual loss and patients also typically suffer with chronic disabling headaches.

This trial has been designed to evaluate the efficacy and safety of a new release formulation of exenatide (Presendin) in the reduction of intracranial pressure (ICP) in patients with IIH. The primary outcome will be determined by change in ICP, as measured by lumbar puncture (LP).

Eligible, consenting patients will be randomised in a ratio of 1:1 to receive Presendin or placebo as a weekly dose for 24 weeks.

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INVESTIGATOR SIGNATURE PAGE

I, the undersigned, have read and understood the protocol and am aware of my responsibilities as an Investigator. I agree to conduct the study in accordance with this protocol, the Trial Reference Manual and any subsequent amendments, the Declaration of Helsinki, ICH GCP guidelines, and the laws and regulations of the country in which the study is being conducted.

Investigator Name and Qualifications: _____

_____ _____

Investigator Signature Date

[Investigator Affiliation]

INVESTIGATOR INFORMATION PAGE

Details will be provided in the Investigator Site File

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ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCRF	Electronic Case Report Form
BMI	Body Mass Index
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DGM	Data-Generating Models
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
EU	European Union
GCL	Ganglion Cell Layer
GLP-1	Glucagon Like Peptide-1
HVF	Humphrey Visual Field
ICF	Informed Consent Form
ICP	Intracranial Pressure
IAC	Independent Adjudication Committee
ICH-GCP	International Council of Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
IIH	Idiopathic Intracranial Hypertension
ITT	Intention-to-Treat
LP	Lumbar Puncture
MAR	Missing At Random
MD	Mean Deviation
MHD	Monthly Headache Days
NRS	Numeric Rating Scale
OCT	Optical Coherence Tomography
PK	Pharmacokinetic
PP	Per Protocol
QTcF	QT Interval corrected according to Fridericia's formula
RNFL	Retinal Nerve Fibre Layer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	36-item short form survey
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
VFQ-25-10 item	Visual Function Questionnaire-25 and 10-item supplement

PROTOCOL SUMMARY

Rationale

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends.

IIH has significant associated morbidity and reduced quality of life. Elevated ICP causes papilloedema universally at disease onset and can lead to permanent visual loss. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Besides risk of visual loss, the most disabling aspect for patients is severe chronic headaches driven by elevated ICP. Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but the failure rates are high and frequent complications and side effects occur.

A modified release formulation of exenatide (Presendin) has been developed and this trial has been designed to evaluate the efficacy and safety of Presendin in IIH. The modified release formulation has been chosen to enable a once weekly dosing.

Objectives

Primary Objective

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

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

Secondary Objectives

To determine the effect of Presendin on change in:

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

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

Safety Objectives

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

Exploratory Objectives

To determine the effect of Presendin on:

- Macular ganglion cell layer/complex thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes (PROs)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Endpoints

Primary Endpoint

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

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

Secondary Endpoints

- Perimetric Mean Deviation
- Retinal nerve fibre layer thickness
- Optic nerve head size
- The number of monthly headache days (MHD). Monthly headache days will include 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 require acute headache analgesia.
- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

Safety Endpoints

- Vital Signs

- Adverse events: Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs)
- Resting 12-lead ECG
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

Exploratory Endpoints

- Macular ganglion cell layer/complex thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes:
  - Visual Function Questionnaire-25 and 10-item supplement (VFQ-25-10 item supp)
  - Headache Impact Test -6 (HIT-6)
  - 36-item short from survey (SF-36)
  - EuroQol -5 dimension -5 level (EQ-5D-5L) survey
  - Patient Global Impression of Change (PGIC)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Trial Design

This is a randomised, placebo-controlled, double-blind, multi-centre trial requiring 240 adult randomised patients with IIH to determine the efficacy and safety of Presendin.

Exenatide pharmacokinetics will be conducted and population PK modelling may be performed.

Consenting patients with a diagnosis of IIH will enter a 1-week screening period, in which there will be no investigational treatment, to gather baseline measurements and to check eligibility. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period due to the real risk of visual loss. Headache diaries designed to measure headache frequency have

successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Wall, 2014, Markey, 2017 and Mollan, 2021]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

At the screening visit, patients will be provided with training on the self-administration of the trial medication and provided with a leaflet to take home. Patients will be asked to self-administer one (1) dose of placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed a screen failure and will not be randomised into the trial. Eligible patients will then be randomised to receive either Presendin or matching placebo for 24 weeks in a 1:1 ratio. After completion of the randomisation period patients will have an end of treatment clinic visit. Five weeks after the end of treatment visit, an end of trial safety follow up telephone visit will also be performed.

The duration of the double-blind treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy over a 3-month time horizon. Additionally, an alternative off label drug used in IIH (acetazolamide) evaluated efficacy over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk. The duration of the trial for each patient will be up to 30 weeks, which includes a 1-week screening period, a 24-week randomised double-blind treatment period, and a treatment follow-up period of 5 weeks.

Trial Population

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of new IIH by consensus criteria (see Section 16.2, Appendix 2), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Newly diagnosed patients with screening commenced no more than 4 weeks after the diagnostic LP
4. Lumbar puncture opening pressure ≥ 25 cm cerebrospinal fluid (CSF) at diagnosis
5. Presence of bilateral papilloedema (Frisén grade ≥1). Verification of papilloedema by the OCT Reading Centre. Where there is uncertainty fundus

photography and/or ultrasound scan (B scan) of the optic nerves should be conducted for evaluation by the Independent Adjudication Committee (IAC)

6. Perimetric Mean Deviation (PMD) defined as between -2 to -7 decibels (dB) in at least one eye. Eyes meeting this criteria will defined as 'study eyes'
7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses, (reliability confirmed by the Visual Field Reading Centre) in study eyes
8. Two or more headache days over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period
9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.8, Appendix 8 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Able to provide written informed consent

    Note: This would restrict the ability of vulnerable patients, such as inmates of psychiatric wards, prison or state institutions, with commitment to an institution or a patient who is detained or committed to an institution by a law court or by

legal authorities to be included on the grounds that informed consent could not be assumed.

Patients must not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusion criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth or seventh nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
6. 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

Vision related exclusion criteria:

7. Any disease other than refractive error that causes visual loss in the study eyes. Where there is uncertainly this would be determined by the Independent Adjudication Committee [IAC]
8. Refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in study eyes. In addition, participants with myopia of worse than -6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes. Where there is uncertainly this would be evaluated by the Independent Adjudication Committee [IAC]

Headache related exclusion criteria:

10. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

11. Untreated previously diagnosed obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
12. Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
13. COVID-19 vaccine within 2 weeks prior to screening
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which may affect the safety of the patient
16. History of drug-induced immune-mediated thrombocytopenia from exenatide products
17. Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
18. Using any glucose-lowering medication
19. Currently taking warfarin
20. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)
21. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
22. Any of the following abnormalities in clinical laboratory tests at screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
23. Using recreational or illicit drugs at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
24. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period

25. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
26. Any contraindication to lumbar puncture procedure in the opinion of the investigator
27. Has participated in any other interventional trial within 1 month prior to the screening visit.
28. Is pregnant or breastfeeding

Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2

Trial Assessments

Table 1: Time and Events

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Informed consent	X											
Inclusion/Exclusion criteria	X	X (review)										
Demography (sex, age, ethnicity)	X											
Medical & Ophthalmic History	X											
Concomitant medication history	X											
Headache history	X											
Concomitant medication review		X	X	X	X	X	X	X	X	X		X
Headache preventative medication review	X	X	X	X	X	X	X	X	X	X		X
Train and dispense headache diary	X											
Review headache diary[1]		X	X	X	X	X	X	X	X	X		
Vital signs[2]	X	X		X	X	X	X	X	X	X		(X)
Height	X											

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Body weight and BMI	X	X			X	X	X	X	X	X		
Adverse Events[15]		X	X	X	X	X	X	X	X	X		X
Physical Examination (T = targeted)	X (Full)	X (T)				X (T)		X (T)	X(T)	X (T)		(X)
Pregnancy Test[3]	X (Serum)	X		X	X	X	X	X	X	X		X
Electrocardiogram	X	X		X	X	X	X	X	X	X		(X)
OCT Imaging	X	X		X	X	X	X	X	X	X	X	
Assessment of Papilloedema Frisén grade[4]	X	X										
Perimetry	X	X		X	X	X	X	X	X	X	X	
Visual Acuity Testing (LogMAR score)	X	X		X	X	X	X	X	X	X	x	
Patient Reported Outcomes (HIT-6, SF-36, EQ-5D-5L, VFQ-25 & 10-item supp)		X			X	X	X	X	X	X		
Health Utilisation Form		X	X	X	X	X	X	X	X	X		
PGIC assessment										X		
Laboratory assessments[5]	X	X		X	X	X	X	X	X	X		(X)

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Pharmacokinetic (PK) sampling[6]		X[7]		X	X	X	X	X	X	X		
Anti-Drug Antibodies (ADA) sampling		X		X	X	X	X	X	X	X		
Lumbar Puncture[8]										X[9]		
Trial medication training[10]	X	X										
Randomisation		X										
Trial medication Dispensing	X	X			X	X	X	X	X			
Trial medication Accountability				X	X	X	X	X	X	X		

1 The screening period must be a minimum of 7 days, up to a maximum of 10 days. Patients who do not meet the eligibility criteria based on diary review at randomisation/baseline (e.g., too few headache days or unacceptable concomitant medication use) will be considered screen failures; however, if the patient wishes and the Investigator is in agreement, he/she can be re-screened as a new patient. If the screening period exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit. Trial site research team should review diaries remotely on a weekly basis to ensure compliance and follow up any patients with missing data

2 Vital signs to include: blood pressure and heart rate

3 Women of child-bearing potential. Serum pregnancy test to be conducted at screening, thereafter, highly sensitive urine pregnancy tests will be conducted. Visit 11 urine pregnancy test may be conducted at home

4 Frisén grade will be evaluated locally and the presence of papilloedema verified by the OCT Reading Centre at screening to confirm eligibility. Indeterminate cases should be referred to the IAC (and supplemented with fundus photography and ultrasound scan of the optic nerve) to confirm papilloedema prior to randomisation visit

5 Haematology, coagulation, biochemistry and urinalysis

6 All actual sampling times and dosing times will be recorded

7 Baseline Post-dose PK blood sample

[8] The diagnostic LP will be the baseline LP and must be performed in lateral decubitus position. Patients with ICP <25 cm CSF at diagnosis will be excluded

[9] Lumbar puncture to be performed after visual assessment. LP to be performed as per Appendix 1. CSF sample from visit 10 LP will be retained for future potential analysis

[10] Patients will be provided with training on the self-administration of the trial medication. The patient will be asked to self-administer placebo at visit 1 to demonstrate ability to self-inject. Patients who are not comfortable to self-inject will be excluded

[11] If patients discontinue in the randomised double-blind treatment period they will be encouraged to return for all trial visits up to visit 11. If a patient does not want to return for all visits then they will be asked to return at a minimum for visit 11 procedures for safety follow up

[12] In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days

[13] Optional unscheduled visit for visual testing (HVF, OCT, LogMAR) for patients in whom there is concern about visual decline or who perform inadequately or where there is technical failure (more than 15% false positive responses or inadequate performance indicated by the Visual Field Reading Centre for HVF; or OCT imaging not of satisfactory quality as determined by the OCT Reading Centre)

[14] In the event of any abnormal safety assessments identified at end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments

[15] Reporting of AEs/SAEs will continue up to the final follow up visit 11

1. INTRODUCTION

1.1. Background and Rational

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends [Mollan, 2019a]. There is a high rate of repeat hospital admission in IIH (increased by 446% in last decade), reflected in escalating healthcare costs (in England £462 million/year predicted by 2030 [Mollan, 2019a] and more than $444 million in the USA [Friesner, 2011]).

The cause of IIH is not fully understood. Recent research suggests that IIH is a disease of systemic metabolic dysregulation characterised by central adiposity [Hornby, 2017], double the risk of cardiovascular disease in excess to that mediated by obesity [Adderley, 2019] and dysfunctional adipocyte metabolism primed for weight gain [Westgate, 2021]. Patients are also insulin resistant and have a unique hormone signature of androgen excess both systemically and in the cerebrospinal fluid.[O'Reilly, 2019]

Morbidity in IIH is due to the elevated intracranial pressure which can cause severe papilloedema (swelling of the optic nerve) which can ultimately lead to blindness. The risk of permanent visual loss is a major concern in IIH. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Headache is an additional major disabler and affects the majority of IIH patients (over 90%) [Yri, 2014; Markey, 2016; Mulla 2015] in the long term. Headaches significantly reducing quality of life [Mulla, 2015; Digre, 2015] are driven by raised intracranial pressure and often have a migraine- like phenotype (> 90%) [Mollan 2021a].

Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. [Piper, 2015; Mollan, 2018; Hoffmann, 2018]. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but there is a high failure rate and frequent complications. The lack of licenced or targeted treatments in IIH perpetuates poor outcomes for patients. A priority setting exercise was run by patients with IIH (James Lind methodology) [Mollan, 2019c] establishing effective therapy was the top priority from the patient group.

This trial will investigate an alternative therapeutic option for lowering ICP and thereby reducing papilloedema and consequently reducing the risk of visual loss. By reducing

ICP it would also aim to improve headache, improving overall patient quality of life in IIH [Mollan 2021a].

Gut neuropeptides are increasingly being recognised for their role in the central nervous system (CNS). A principal gut neuropeptide is glucagon like peptide-1 (GLP-1), which is known to stimulate insulin release, proliferation of pancreatic beta cells and control of glucose regulation in diabetes [Campbell, 2013]. Exenatide is a GLP-1 receptor agonist. It has also been shown to have some actions in the CNS; GLP-1 is involved in regulating satiety and weight through signalling at the hypothalamus [Astrup, 2009]. There is also evidence that GLP-1 may have a role in fluid secretion. In the renal proximal tubule GLP-1 acts to reduce sodium resorption to promote diuresis [Gutzwiller, 2004; Websky, 2014]. The choroid plexus is the fluid secreting structure within the brain producing the majority of CSF. The structure of the choroid plexus epithelial cells is analogous to an inverted renal proximal tubule with a similar mechanism of secretion and hence GLP-1 receptor agonists may also reduce CSF secretion in the brain, leading to a decrease in ICP in patients with IIH.

Exenatide as well as other GLP-1 receptor agonists can lead to weight loss. In diabetic patients, weight loss of 2.8 - 4.4 kg has been reported over 6 months [Di Dalmazi 2020; Pujante 2012]. Whilst in non-diabetic overweight and obese patients exenatide caused sufficient weight loss between 2.0 – 5.1 kg [Moreno 2012]. In overweight and obese patients with polycystic ovarian syndrome exenatide led to 2kg more weight loss compared to placebo in over 12 weeks [Liu 2017]. Weight loss with exenatide therapy is increased in the setting of calorie restriction [Rosenstock 2010]. Weight loss is a desirable effect of exenatide as weight loss is therapeutic in IIH. Changes in body weight will be monitored during the trial and the impact on outcomes measures evaluated.

Exenatide is the active ingredient in Byetta, an immediate-release (IR) formulation and Bydureon, an extended-release (ER) formulation. These have been licenced for use in adults with type-2 diabetes since 2005 and 2014, respectively. Therefore, there is a wealth of available safety data from both clinical trials and real-world experience. Exenatide has been identified as a potential candidate for the treatment of neurological conditions involving raised ICP and a polylactic-co-glycolic acid (PLGA) ER exenatide formulation under the name Presendin, has been developed by Invex Therapeutics for the treatment of IIH.

Byetta has a known issue of rapid elimination of the product when given to humans, and because of this it needs to be administered twice daily to achieve its pharmacological effects. The data on file from the IIH Pressure trial has shown that in patients with IIH, exenatide administered twice daily was well tolerated and produced a positive effect on reducing CSF pressure. However, it is considered that the immediate release formulation

of exenatide is not ideal for treating patients with IIH on a long-term basis. Presendin has been developed as an extended release formulation to allow for a reduction in dosing frequency to once weekly and more consistent therapeutic plasma levels.

This trial is designed to investigate the efficacy and safety of a modified release formulation of exenatide (Presendin) in patients with IIH.

Intracranial pressure

IIH is a debilitating condition characterised by raised ICP, which is clinically measured by LP [Mollan, 2018]. The units for measurement of LP are cm CSF and cm H_2O and these should be thought of as interchangeable and reflect the measurement of the height of the CSF column at LP. The measurement must be taken in the lateral decubitus position. Lumbar puncture is conducted to make a diagnosis of IIH. Lumbar puncture may be conducted in a clinical setting during the disease course to both monitor and treat the condition. Frequent therapeutic LPs are no longer recommended by the International IIH guidelines [Mollan, 2018]. This is because LP can be traumatic for patients and can occasionally cause significant complications (meningitis, spinal haematoma, pain) [Wright, 2012]. Hence, unnecessary LP's should be avoided. In some patients LP can alter other outcome measures, including measurements of papilloedema and headache [Yiangou, 2019]. Hence ideally, LP should be performed after these measures and symptoms have been assessed. Lumbar puncture can cause post-dural puncture headaches. The risk is 9-36% using a traumatic needle and 3-19% using an atraumatic needle [Wright, 2012]. Post-dural puncture headaches typically last less than a week but in some patients this can be longer [Yiangou, 2019]. Lumbar puncture pressure assessment of ICP reflects disease activity and is a useful and recognised outcome measure that has been utilised in other IIH trials [Markey 2020; Mollan 2021b].

Due to the invasive nature of LP, non-invasive measures of ICP are valuable. The majority of techniques historically evaluated as non-invasive surrogate measures of ICP lack sufficient quantification to be used clinically or in clinical trials. Optical coherence tomography (OCT) measures of the optic nerve have been shown to provide a useful surrogate measure to quantify changes in ICP [Vijay, 2020]. For example, at 12 months, Vijay *et al* showed that a change in optic nerve head height of 50 µ predicted a 5 cm CSF change in ICP [Vijay, 2020].

Visual Function

Perimetry is used to measure visual function in IIH clinical practice. This is assessed using a Humphrey Field Analyzer (program 24-2 SITA standard using a size III white stimulus) test. Patients are often unaware of their visual field loss until this becomes more

severe and compromises daily activities. In patients with severe papilloedema optic atrophy can develop (measured objectively as loss of the macular ganglion cell layer on OCT imaging) and the loss of visual field becomes permanent. Patients at risk of rapidly progressive visual loss (also termed fulminant IIH) should receive emergency surgical intervention (most commonly a CSF shunt operation) [Mollan, 2018]. Patients requiring emergency surgery will not be recruited into this trial. Medical therapy is used to treat those IIH patients not requiring emergency surgical intervention and will be included in this trial. But it is expected that approximately 5-10% will go on to need more aggressive intervention.

Measuring visual function with perimetry has a number of challenges in IIH which need to be carefully considered. The visual field test is dependent on technician and patient performance and can be prone to variability and inaccuracy [Cello, 2016; Wall, 2016]. Patients can perform poorly on automated perimetry [Cello, 2016], and there is a learning effect [Kutzko, 2000; Wall, 2016]. There are further confounding factors when considering interpretation of automated visual field testing in IIH. The high prevalence of functional vision loss, presenting as non-organic visual fields results in this disease, may bias trial outcomes [Kutzko, 2000; Ney, 2009]. Additionally, impaired executive function and attention deficits have been noted in IIH [Sørensen, 1986], and have been shown to impair performance of visual field testing in IIH [Grech, 2021].

The protocol has been designed with these challenges in mind and visual field testing performance will be assessed at trial entry and throughout with opportunity for repeated assessment if there is performance failure (a performance failure is defined as a substantial worsening of the perimetric mean deviation due to human factors rather than visual damage) [Cello, 2016].. The visual fields will be assessed by the Visual Field Reading Centre.

Papilloedema by change in optic nerve head size measured by OCT imaging.

Papilloedema is a reliable sign of raised ICP [Dunn, 2002]. Change in papilloedema has been used by all the randomised control trials in IIH to date to determine clinical improvement [Ball, 2011; Wall, 2014; Mollan 2021b]. Change in papilloedema has been graded by experts using the Frisén classification, although it is more reliably measured by OCT imaging [Ball, 2011; Wall, 2014]. Professional bodies and the literature endorse the use of OCT imaging for monitoring papilloedema in IIH [Mollan, 2018].

OCT imaging measures various aspects of the optic nerve. The retinal nerve fibre layer (RNFL) and optic nerve head volume are measurements that both reflect swelling of the optic nerve and hence the extent of papilloedema. Measures of macular volume can quantify the ganglion cell layer (GCL) thickness which reflects axonal loss. Optic nerve

head measures on OCT correlate with visual field sensitivity loss [Salgarello, 2001]. Analysis has shown that OCT measures of the RNFL significantly reflect changes in visual field perimetric mean deviation (MD) (for every 10µm increase in RNFL there was associated with a 0.6dB decrease in MD) [Rebolleda, 2009]. Optical coherence tomography measures of the macula volume have been shown to predict axonal loss of the optic nerve [Albrecht, 2017]. Most importantly, ganglion cell volume has been shown to significantly correlate with the Humphrey visual field MD [Vijay, 2020]. This indicates that the GCL can be measured to reflect visual function. In other neurological diseases OCT has also been found to measure neuronal loss and correlated with visual loss [Petzold, 2010]. In summary, OCT assessment of the optic nerve and GCL represent objective measures of papilloedema and optic nerve axons which reflects visual function.

The scan quality can be compromised if the automated software segmentation of the OCT is not accurate. This occurs particularly in those optic nerves with more pronounced papilloedema [Aojula, 2018]. Hence the quality and segmentation of all OCT scans will be assured by the OCT Reading Centre and scans will be repeated if of insufficient quality.

Headache

Headache is the predominant presenting feature in IIH [Mollan, 2019a]. Patient morbidity is high because of disabling headaches and they have been found to be the key driver for poor quality of life [Mulla, 2015; Digre, 2015]. Research into headache treatments were endorsed as clinically relevant by a priority setting partnership which included the opinions of the patients' carers and physicians [Mollan, 2019c].

It has been well documented that headache characteristics in IIH are typically migraine-like (up to 90%) [Mollan, 2019b; Mollan 2021a]. The headache location can be halo-cranial, frontal, temporal or parietal with features including nausea, throbbing pain, photophobia and phonophobia [Yri, 2015]. A Danish trial of 44 IIH patients noted that 82% of patients had migraine-like attacks [Yri, 2014]. A prospective trial in 52 IIH patients in the UK characterised 80% of headaches as migraine-like [Yiangou, 2019]. As reported by the Idiopathic Intracranial Hypertension Treatment Trial, US, the headache phenotype was recorded as migraine or probable migraine in 68% of 144 patients with active IIH [Friedman, 2017]. A retrospective trial in Iran in 68 IIH patients characterised migraine-like headaches in 63% [Sina, 2017]. Other headache characteristics are typically tension-type or unclassified [Mollan, 2019b].

Hence whilst IIH headaches are not diagnostically the same as migraine according to the International Classification of Headache Disorders, 3rd edition Beta, they are very similar

in character [Olesen, 2018]. The International Headache Society core outcomes for migraine are therefore applicable to IIH headaches [Tassorelli, 2018].

Headache in active IIH is driven by ICP. This is evidenced by the fact that removal of CSF fluid results in improved headache severity. In a prospective cohort study, headache severity improved in 71% following a standardised LP [Yiangou, 2019]. Ninety-five percent of IIH patients had improvement in headache symptoms at 1 month following shunt placement [Daou, 2020]. Weight loss leading to reduction in ICP also significantly reduced headache [Sinclair, 2010].

Medications that reduce ICP have been shown to modulate headache. In an open label trial using topiramate and acetazolamide, both of which are known to modulate ICP [Scotton, 2019], relief of headache was reported after a mean treatment period of 3.75 months in the topiramate group and 3.3 months in the acetazolamide group [Çelebisoy, 2007].

Importantly, headache measures (severity and monthly headache days) in IIH significantly correlate with changes in ICP [Mollan 2021a]. The IIH weight trial [Mollan, 2021b], a randomised controlled parallel group multicentre trial in the United Kingdom, investigates weight management methods in IIH. Participants with active IIH (evidenced by papilloedema) and a body mass index (BMI) $\geq$35kg/m^2 were recruited. The primary outcome was ICP as measured by LP opening pressure at 12 months, with secondary outcomes of ICP at 24 months and headache outcomes at 12 and 24 months. Headache severity was correlated with ICP at baseline; change in headache severity and monthly headache days correlated with change in ICP at 12 months. Importantly those with the greatest reduction in ICP over 12 months had the greatest reduction in headache frequency and severity. This implies that treatment of ICP should improve headache in IIH.

The following headache outcomes are clinically relevant and are recommended by the American Headache Society [American Headache Society] and International Headache Society to identify patients who are benefiting from treatments. Headache outcomes are derived from a 28-day diagnostic headache diary. This is used in clinical trials to prospectively collect daily information on headache occurrence, severity, associated symptoms, and use of acute analgesic medications.

Although a headache diary is typically over 28 days, for IIH headache it was felt necessary to shorten this period during which no other planned assessments of vision were scheduled. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be

representative [Mollan 2021b]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

Monthly headache days

Monthly headache days (MHD) will include 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 require acute headache analgesia. This is the most relevant and objective measure of headache.

Moderate to severe monthly headache days

A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications. This outcome captures the more disabling headaches.

Moderate to severe MHD was recently reported as the primary endpoint in a prospective open label study providing evaluation of the effectiveness of erenumab, a calcitonin gene-related peptide (CGRP) monoclonal antibody, to treat headaches in IIH patients [Yiangou, 2021]. It is also used to measure headache in other secondary headache conditions such as persistent post traumatic headache [Aojula 2018; Ashina, 2020].

Headache responder rate (≥50% reduction in MHD)

Headache responder rate (≥50% reduction in MHD) is the proportion of patients achieving at least 50% reduction in the mean number of MHD, of any intensity, from baseline to the defined trial end point. This criterion is clinically relevant as it is used as an empirical review for continuing or discontinuing headache therapy [Diener, 2020]. Responder rates can be used in meta-analyses of placebo controlled randomised controlled trials.

Headache responder rate (≥50% reduction in moderate to severe MHD)

Headache responder rate (≥50% reduction in moderate to severe MHD) is the proportion of patients achieving at least 50% reduction in the moderate to severe MHD from baseline to the defined trial end point. It is well recognized that 50% responder rates may not fully capture the benefits of treatment [Matharu, 2017]. For example, a patient may improve from a disabling 20 severe headache days per month to 11 moderate headache days per month. Despite this considerable clinical benefit, such a patient would not be considered a responder because headache days were not reduced by ≥50%, and as a result might lose access to beneficial treatment. Hence, responder rates of ≥30% are also

important [Vernieri, 2019]. In IIH, a disorder of chronic severe headaches, a clinically meaningful treatment responder rate has not been definitively established, although the International Headache Society Clinical Trials Subcommittee has suggested the use of a ≥30% reduction from baseline for chronic migraine.

Headache severity

Headache severity is an important measure and impacts quality of life. It is vital to consider some treatments which benefit headache may not reduce the MHD but if the severity is markedly improved this will lead to great overall functional benefit to the patient and is clinically relevant [Silberstein, 2008]. Recording the decrease in intensity is an indicator of reduced disability, which is clinically meaningful.

Monthly use of acute headache rescue medications

Use of acute headache analgesics reflects a judgement of the inefficacy of the test treatment; hence it is a helpful secondary outcome. In Sinclair *et al.* reduction in analgesic days was significant and associated with clinical remission of IIH [Sinclair, 2010]. Additionally, a high portion of IIH, up to 48% [Yiangou, 2021] have medication overuse and medication overuse headache, and reduction in analgesic days mitigates these. Reduction in monthly use of acute headache analgesic is an additional endpoint that contributes to clinically meaningful results.

Quality of life in IIH

IIH has a detrimental effect on all aspects of the patient's quality of life; the majority of which is driven by headache [Kleinschmidt, 2000, Mulla, 2015; Daniels, 2007; Digre 2015]. IIH also impacts visual function with PMD correlating with quality of life [Bruce 2016]. Patient reported outcomes in clinical trials are essential not only to permit health technology assessments and cost effectiveness analysis, but also as key outcomes for a therapy's effectiveness [Deiner, 2019]. There is currently no IIH disease specific quality of life outcome measure.

Whilst there are differences in the choice of the tools used in the trials, they all commonly used the short-form 36 health survey (SF-36) [Mollan, 2021, Wall, 2014, Digre, 2015; Bruce, 2016; Ball, 2011]. The physical component score of the SF-36 has been shown to correlate significantly with changes in ICP [Grech 2021]. The EuroQol –5 dimension (EQ-5D-5L) [Euroqol, 1990] is typically employed for health technology assessments and cost effectiveness [Ottridge, 2017; Ball, 2011]. Using the EQ-5D-5L in isolation may lack sensitivity as compared to the SF-36 for IIH. The National Eye Institute Visual Function Questionnaire-25 and 10-item supplement [Mangione, 2001]

has also been utilised to assess visual related quality of life in IIH and is associated with improvement in visual field [Bruce 2016; Mangione 1998; Raphael 2006]. The 10-Item neuro-ophthalmic supplement was found to be significantly discriminating in a previous IIH drug trial [Wall 2014].

Pharmacokinetics

Exenatide pharmacokinetics will be conducted and population PK modelling may be performed.

1.1.1. Name and Description of the Investigational Product

Patients will receive active treatment, Presendin, or matching placebo.

Presendin is a modified release formulation of exenatide. Exenatide is a GLP-1 receptor agonist currently used in the management of type 2 diabetes. Presendin consists of a drug part (white or greyish white powder in a clear vial) and a diluent part (colourless liquid in a pre-filled syringe). The drug part is suspended in the diluent part solution and administered as a suspension. The patient or responsible person will be responsible for rehydrating the product for injection. Presendin is administered as a once weekly SC sustained-release injection containing 2.0 mg exenatide. Matching placebo will also be supplied as 2 parts, as visually identical vial and pre-filled syringe. The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. Placebo is administered once weekly as a SC injection.

1.1.2. Non-clinical Studies

Exenatide, the active ingredient of Presendin, has been previously developed and licensed as Byetta for the treatment of type 2 diabetes. A wealth of historical toxicological and pharmacological safety data is available in the public domain. Please see the Investigator's brochure for data from rat and mouse studies which have investigated the Presendin formulation of exenatide.

In vitro and *in vivo* data suggests that the choroid plexus, the CSF secreting structure in the brain, contains GLP-1 receptors [Ast 2020]. Preclinical studies in rodents demonstrate that GLP-1 agonists can regulate cerebrospinal fluid dynamics and reduce ICP [Botfield, 2017].

Nonclinical pharmacology studies have shown that exenatide and GLP-1 agonists bind to and stimulate GLP-1 receptors equipotently. Due to the ability of exenatide to affect fluid homeostasis in the kidney, it was investigated for its potential to modulate CSF secretion

and reduce ICP in rats. A single SC injection of exenatide rapidly (within 30 minutes) reduced ICP and maintained lower ICP for 6 days of dosing, suggesting that GLP-1 receptor agonists could provide an alternative treatment for conditions with raised ICP [Botfield, 2017].

Exenatide was subjected to full toxicological assessments during its nonclinical development programme, details of which are publicly available in the Byetta® Product Monograph, 2019 and the FDA Pharmacology Review, June 2004 (Section 15). In summary, no lethality or serious toxicity was observed in mice, rats and monkeys following single doses up to 1500 µg/kg, 3000 µg/kg and 5000 µg/kg respectively. In repeat-dose toxicity studies decreased body weight gain and food consumption, a known pharmacological effect of exenatide, were observed in all studies. Exenatide caused no mortality or target organ toxicities in mice, rats and monkeys at doses up to 760µg/kg/day (182 days), 250 µg/kg/day (91 days), or 150 µg/kg/day (273 days) respectively. Reproductive toxicity data from animal studies showed that Byetta had a toxicological effect on foetal development at three times the human exposure levels in treatment of diabetes. A summary of the findings of the exenatide toxicological assessment programme is presented in the Investigator Brochure for Presendin.

1.1.3. Clinical Studies

Exenatide has undergone extensive healthy volunteer studies and clinical trials for over 15 years. It is licensed as a formulation for SC injection to be used in conjunction with diet and exercise to improve glycaemic control in adults with type 2 diabetes. Details of the trials conducted on exenatide, SC injection formulation, are presented in the Byetta Product Monograph (Section 15). Data from these studies are notable as the dose of exenatide to be used in the indication of IIH is intended to produce exposure levels not exceeding those experienced by patients receiving Byetta. It is anticipated that the proposed therapeutic dose of exenatide, in the modified release formulation Presendin, for treatment of IIH will be within the approved dose range of Byetta, achieving a level of total systemic exposure comparable with the immediate release Byetta formulation. Therefore, safety data available from the Byetta clinical development program are considered relevant and supportive of exenatide development in IIH.

The efficacy of exenatide (Byetta) was evaluated in a Phase 2 randomised, placebo controlled, double-blind trial of exenatide in patients with active IIH (IIH:Pressure Trial). Sixteen patients with a diagnosis of active IIH (LP opening pressure >25 cm CSF and papilloedema) were identified and recruited to the trial. Participants had a telemetric ICP monitor implanted and were randomised to either exenatide (first dose was 2. 0 mcg followed by 10 mcg BD sub-cutaneous) or a matched placebo; allocation was 1:1. The treatment duration was 12 weeks. The trial was powered to seek significance to at least

alpha < 0.1 and power at least 80% using equal group sizes. Data was analysed by hierarchical regression analysis. 16 participants were recruited, 15 were randomised and completed the study. At baseline the mean age was 28 ± 9 years, BMI 38.1 ± 6.2 kg/m2, ICP 23.5 ± 3.9 (equivalent to 32.0 ± 5.3 cm CSF). The primary outcome, change in intracranial pressure between arms, was significant: at 2.5 hours -4.2 ± 2.1 mmHg (equivalent to 5.7 ± 2.9 cm CSF), p=0.04, at 24 hours -4.7 ± 2.1 mmHg (equivalent to 6.4 ± 2.9 cm CSF), p=0.03, and at 12 weeks -4.1 ± 2.2 mmHg (equivalent to 5.6 ± 3.0 cm CSF), p=0.05. A significant reduction in monthly headache days was also observed amongst those on exenatide (-7.7 ± 9.2, p-0.069). LogMar visual acuity also significantly improved in the exenatide treated arm (-0.1 ± 0.05, p=0.036). No significant weight loss was observed in either arm and hence weight change is unlikely to have contributed to the reduction kin ICP observed. Exenatide was safe and well tolerated: no treatment related SAE's were reported, 8 adverse events were reported in those taking exenatide. The most frequent adverse event, amongst those taking exenatide, was nausea (7 reports), the majority of these were mild and all reports were self-limiting. There were no patient withdrawals due to adverse events.

1.1.4. Trial Conduct

This trial will be conducted in accordance with the requirements of this document (the Clinical Trial Protocol), the Trial Reference Manual and also in accordance with the following as per country specific requirements:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)
- The United Kingdom Statutory Instrument 2004 No. 1031 and UKSI 2006 No.1928
- European Union Directives 2001/20/EC and 2005/28/EC
- United States Code of Federal Regulations Title 21
- The Australian Therapeutic Goods Act, 1989, amended December 2020 and Therapeutic Goods Regulations, 1990, amended January 2021
- Other country specific laws and regulations
- Any amendments to these regulations

The safety of the study participants is of primary importance, and risks of involvement in the study, in particular with added challenges due to global pandemia of COVID-19, will be weighed against anticipated benefit for the study participants and society.

Study sites may continue to recruit new participants, if deemed appropriate on benefit-risk assessment as described, and provided that ALL of the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage studies and participants effectively and in compliance with the protocol.
- Upon discussion with the sponsor, medical monitor, or designee, the study site has confirmed that appropriate safety monitoring can take place, in compliance with the protocol.
- Data will continue to be entered into the electronic Case Report Form (eCRF) and queries resolved in a timely manner.
- The site monitor is able to access the study site to perform onsite monitoring or is able to perform remote monitoring of data.

The sponsor recognizes that COVID-19 presents an increased risk for all participants. Due to the potential impact of COVID-19 on multiple organ systems, the sponsor recommends the following dose modification and management plan for participants with confirmed or suspected COVID-19 while receiving treatment with Presendin.

All confirmed or suspected COVID-19–related adverse events (AEs) must be recorded in the eCRF and the Serious Adverse Event (SAE) Report Form if the event meets the seriousness criteria. SAEs are reportable to the sponsor immediately without undue delay after becoming aware of the event. All study-drug interruptions or modifications must be recorded on the AE and drug administration eCRFs.

If a participant is diagnosed with COVID-19 or is suspected to have COVID-19, continuation of study drug, and any dose modifications should be assessed on a case-by-case basis by the investigator, depending on the participant's health status, and discussed with the medical monitor if needed. The COVID-19 infection should be managed as per local treatment guidance.

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1.2. Risk/Benefit Assessment

1.2.1. Benefits

1.2.1.1. Identified

Improving IIH morbidity with new therapeutics is clearly identified as an unmet need. However, as this trial will study the use of an experimental, new drug against a placebo (no drug with a proven effect will be given as part of this study), no benefit can be assessed as identified.

1.2.1.2. Potential

Immediate-release exenatide (Byetta) was tested in the indication of IIH as a phase 2 study. Reductions in ICP from baseline were observed in the exenatide group 2.5 hours, 24 hours and 12 weeks after initiation of dosing (the level of significance was establish a prior as $p<0.1$).; the reduction achieved statistical significance at 24 hours ($p=0.042$; t-test). This suggests a potential benefit of exenatide, the active ingredient of Presendin, in treatment of IIH. The IIH Evolve trial is the first Phase 3 trial aiming to bring to market, and thus into clinical practice, a new drug to treat IIH.

New treatments for IIH are a top priority as identified by patient groups. [Mollan 2019c]. Patients receiving the active treatment during the randomised period may benefit by experiencing an improvement in their IIH symptoms, although this cannot be guaranteed.

1.2.1.3. Expected

For the participants, there is no guarantee of an expected benefit from taking Presendin. However, patients in research trials typically benefit from increased disease monitoring and access to health care professionals.

1.2.2. Risks

Safety data for Presendin (exenatide) is based on the IB (Peptron Inc.). Warnings include pancreatitis and hypoglycaemia when used in combination with a sulfonylurea, renal impairment, severe gastrointestinal disease, and hypersensitivity.

Invex Therapeutics has considered these warnings and has defined eligibility criteria to ensure patient safety is paramount. As such patients with known contraindications to GLP-1 agonists, such as pancreatitis, ketoacidosis, severe gastrointestinal disease and renal impairment, will not be included. Additionally, diabetic patients receiving glucose lowering medication will be excluded.

An Independent Adjudication Committee (IAC), as described in Section 14.5, will assist the Investigators (when required) with the eligibility criteria of the patients to be enrolled, and also to determine treatment failures to ensure patient safety and the efficacy of the trial

1.2.2.1. Identified

The active ingredient of Presendin, exenatide, has been used in clinical practice for over 15 years. The most common adverse reactions experienced with exenatide in patients with other diseases under study (namely diabetes mellitus type 2) are nausea, hypoglycaemia (only when used with other glucose lowering drugs, but these patients are excluded from the trial), vomiting, diarrhoea, feeling jittery, dizziness, headache and dyspepsia. There is limited clinical data about Presendin itself, therefore the presented risk are based on the data available for a different extended-release formulation of the same active ingredient (exenatide). Based on that, the possible risks related to Presendin treatment are not all known. T following side effects have been reported (in patients with diabetes mellitus type 2) and identified as risks associated with the use of extended-release exenatide.

Very common: more than 10 out of 100 persons treated

- Hypoglycaemia (with sulphylurea)
- Nausea
- Diarrhoea

Common: 1 to 10 out of 100 persons treated

- Injection site erythema
- Injection site pruritus
- Asthenia
- Vomiting
- Headache
- Dizziness
- Dyspepsia
- Abdominal pain
- Abdominal distension
- Gastrooesophageal reflux disease
- Constipation
- Flatulence
- Decreased appetite
- Hypoglycaemia (with insulin)

- Pruritus and/or urticaria
- Fatigue

Uncommon: 1 to 10 out of 1000 persons treated

- Dehydration
- Dysgeusia
- Somnolence
- Intestinal obstruction
- Eructation
- Hyperhidrosis
- Alopecia
- Injection site rash
- Altered renal function (including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine)

Rare: 1 to 10 out of 10000 persons treated

- Anaphylactic reaction
- Feeling jittery

The safety of the study drug, Presendin, has been investigated in two previous clinical studies involving healthy volunteers and diabetic patients, altogether 103 participants. Presendin has not been tested in IIH. The table below represents the expected side effects reported with Presendin given during a Phase 2 Presendin study to participants who received a similar dose of Presendin (1.6 mg Presendin every week). These studies are detailed in the Presendin IB.

Side effects	**Percentage participants with an adverse reaction**
Injection site induration	57.1%
Injection site pruritus	23.8%
Injection site mass	4.8%
Injection site erythema	4.8%
Nausea	9.5%

Dyspepsia	9.5%
Diarrhoea	4.8%
Decreased appetite	4.8%
Rash	4.8%
Itchy Rash (Urticaria)	4.8%

1.2.2.2. Potential

There may be side effects that are not expected or not previously known, and these have the potential to be severe and/or serious. There is a potential risk of allergic reaction (anaphylaxis) that can be severe and/or serious.

1.2.2.3. Expected

Presendin is a new formulation of exenatide and is used in a new indication, all reported serious adverse reactions will be considered unexpected for the purpose of safety reporting.

A Data Safety Monitoring Committee will be reviewing the safety data and will take decisions in order to protect the safety of participants.

2. OBJECTIVES

2.1. Primary Objective

To determine the efficacy of Presendin administered subcutaneously once weekly for 24 weeks to patients with IIH, as determined by change in ICP, as measured by LP at baseline and at 24 weeks.

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

2.2. Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation as measured by Humphrey Visual Field analysis (24-2 SITA-Standard)
- Papilloedema by change in optical coherence tomography (retinal nerve fibre layer (RNFL) thickness and optic nerve head size)
- Monthly headache days (MHD)
- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

2.3. Safety Objective

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

2.4. Exploratory Objectives

To determine the effect of Presendin on:

- Macular ganglion cell layer/complex thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes
- Body Mass Index
- Body Weight
- Health Utilisation

3. ENDPOINTS

3.1. Primary Endpoint

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

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

3.2. Secondary Endpoints

- Perimetric Mean Deviation
- Retinal nerve fibre layer (RNFL) thickness
- Optic nerve head size
- The number of monthly headache days (MHD). Monthly headache days will include all headache days, defined as those with an onset, continuation or recurrence, any severity or phenotype of headache, lasting at least 30 minutes or which require acute headache analgesia.
- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

3.3. Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), , serious adverse events (SAEs)
- Resting 12-lead electrocardiogram
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

3.4. Exploratory Endpoints

- Macular ganglion cell layer/complex thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes (PRO):
  - Visual Function Questionnaire-25 and 10-item supplement
  - Headache Impact Test-6
  - 36-item short form survey
  - EuroQol -5 dimension -5 level survey
  - Patient Global Impression of Change
- Body Mass Index
- Body Weight
- Health Utilisation

4. TRIAL DESIGN

4.1. Summary of Trial Design

4.1.1. Trial Design

This will be a randomised, placebo-controlled, double-blind, multi-centre clinical trial in approximately 240 randomised patients with IIH.

Exenatide pharmacokinetics will be conducted and population PK modelling may be performed.

Randomised, double-blind, placebo-controlled trials are considered the "gold standard" for determining the efficacy and safety of an investigational drug where there is no approved therapy. The trial is designed to compare the efficacy and safety between an investigational drug group and a placebo control group. The randomised, double-blind, placebo-controlled trial design is clinically and methodologically justified because it reduces bias. Use of this trial design will provide reliable evidence that supports the efficacy of the investigational drug, Presendin, for the treatment of IIH.

Participants assigned to the placebo arm are not expected to be exposed to serious or irreversible harm as a result of not receiving unlicensed, potentially (intracranial) pressure lowering medication. There is no licensed therapy to treat IIH. In a previous investigator led randomised controlled trial (RCT), the IIH Treatment Trial (IIHTT), a similar population of IIH patients were recruited. (Wall *et al.*, 2014) Both the previous IIHTT and this trial (IIH EVOLVE) will recruit medically treated IIH patients with analogous eligibility criteria and disease severity (papilloedema and visual fields which are mild to moderately impaired (Humphrey visual field mean deviation between -2dB and -7dB). Akin to this trial, the IIHTT had a 6 month randomisation period (and hence 79 patients were on placebo for 6 months). Of these 79 patients, 6 deteriorated (classified as treatment failures requiring rescue therapy). We would predict that a similar proportion of patients in this trial (6.7%) will require rescue therapy whilst on placebo. No irreversible harm came to those on placebo in the IIHTT and we would anticipate the same in this trial. The pathway to identify treatment failures and initiate rescue therapy in the IIHTT was well described and will be akin to the pathway in this trial to ensure that those patients requiring rescue therapy are rapidly identified and treated. In those patients with treatment failure requiring rescue therapy, the medical team at the site can initiate the most appropriate rescue therapy as per usual clinical practice. This could include adding in an off-licence intracranial pressure lowering medication (as is sometimes done in some current clinical practices) or a surgical procedure if appropriate.

We do not predict a meaningful placebo response rate for the primary outcome measure as this is an objective measure with negligible placebo response observed in previous randomised placebo controlled trials. This is akin for other objectively measured outcomes (including perimetric mean deviation and optical coherence tomography measures) where changes in the placebo arm have been noted in previous IIH studies and interpreted as regression to the mean and disease remission. (NORDIC study working group JAMA 2014). A placebo response is, however, well described for headache outcomes (Mitsikostas DD et al, 2020). In trial participant taking an oral headache preventative therapeutic, this is estimated at 21% and higher for an injected therapy (Autret A et al, 2012). A systematic review of placebo response rates established that the more invasive the placebo the higher the placebo response rate (33.5% for injection vs 27.5% for oral drugs) (Evans K et al, 2021). In the IIH Evolve trial, headaches outcomes are secondary outcome, s measures and as such the IIH Evolve trial is not explicitly powered for these measures, but awareness of the placebo response was considered during the study design.

The trial will begin with a 1-week screening period. Although a headache diary is typically over 28 days, for IIH headache it was felt necessary to shorten this period during which no other planned assessments of vision were scheduled. Headache diaries designed to measure headache frequency have been successfully utilised over shorter time periods in previous IIH trials and noted to be representative [NORDIC, 2018; Mollan, 2021b]. Hence the baseline headache frequency will be calculated over 1 week. Patients will be provided with training on the self-administration of the trial medication from the site trial coordinator and provided with a leaflet to take home at the screening visit. Patients will be asked to self-administer placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed screen failures, and not be randomised into the trial. The purpose of the screening period will be to establish baseline measurements and assess trial eligibility.

The screening period will be followed by a 24-week randomised double-blind treatment period in which patients will be randomised (1:1) to receive a SC dose of either Presendin (containing 2mg of exenatide (active group) or matching placebo (placebo group), self-administered once weekly.

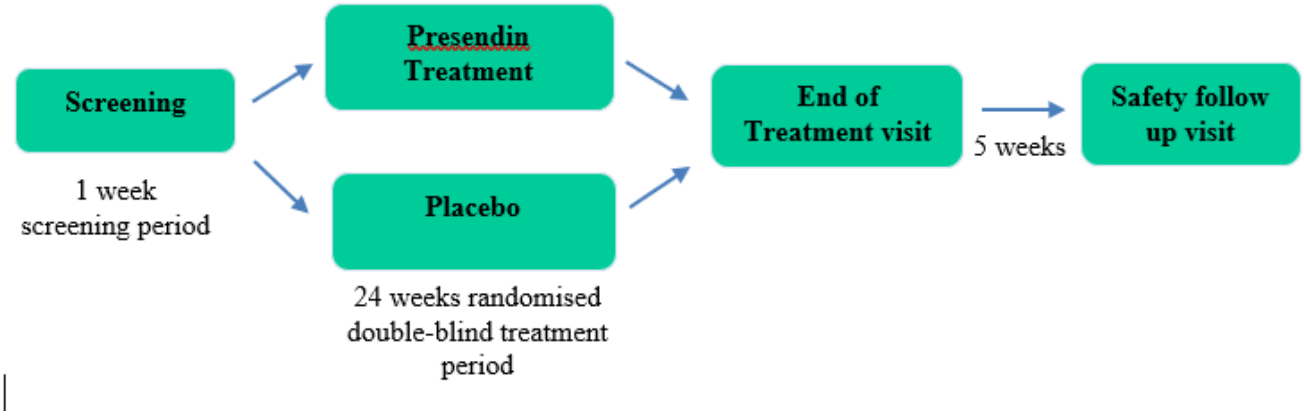
At the end of the randomised treatment period (week 24), all patients will have an end of treatment clinic visit. Five weeks after the end of that treatment visit, an end of trial safety follow-up telephone visit will be performed. In the event of any abnormal safety assessments or ongoing adverse event(s) identified at end of treatment; for example, an abnormal ECG or abnormal routine laboratory results, this visit may be performed at the clinic and a safety follow-up performed as appropriate.

The duration of the randomised treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy by 3 months. Additionally, an alternative off label drug used in IIH (acetazolamide) was evaluated over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk.

Assessments will be performed as outlined in Table 1.

A schematic diagram of the trial can be seen in Figure 1.

Figure 1: Schematic Diagram



4.1.2. Randomisation and Blinding

At the end of the Screening period, eligible patients will be randomised to receive either Presendin or matching placebo in a 1:1 ratio using a computer system to generate randomisation codes.

Investigators and other site personnel, patients, contract research organisation and Sponsor personnel will be blinded regarding the treatment during the randomised period. Only designated unblinded staff, not involved in the operational conduct of the trial, will be aware of the randomisation codes.

The placebo will have the same appearance and reveal no differences, during administration, to either the Investigator or the patient.

4.1.3. Duration of Patient Participation

The duration of the trial for each patient will be up to 30 weeks, which includes a 1-week screening period, a 24-week randomised treatment period and a treatment follow-up period of 5 weeks.

4.2. Stopping Rules

4.2.1. Trial Stopping Rules

There are no trial-specific stopping rules. The Sponsor maintains the right to stop the trial at any point. If this is done, then the Sponsor will provide the Investigators with the rationale for such early termination.

4.2.2. Individual Stopping Rules

Patients will be withdrawn from the trial medication if they are unable to tolerate the trial medication and will continue to attend trial visits as per protocol. See Section 11 for further details. A Data Safety Monitoring Committee (DSMC) will be involved in decisions for patient safety (Section 14.6).

4.3. End of Trial

The end of trial is defined as last patient last visit.

5. TRIAL POPULATION

5.1. Number of Patients

It is anticipated that approximately 350 patients will be required to enter the screening phase for 240 patients to be randomised into the treatment phase.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of new IIH by consensus criteria (see Section 16.2, Appendix 2), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Newly diagnosed patients with screening commenced no more than 4 weeks after the diagnostic LP

4. Lumbar puncture opening pressure ≥ 25 cm cerebrospinal fluid (CSF) at diagnosis
5. Presence of bilateral papilloedema (Frisén grade ≥1). Verification of papilloedema by the OCT Reading Centre. Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerves should be conducted for evaluation by the Independent Adjudication Committee (IAC)
6. Perimetric Mean Deviation (PMD) defined as between -2 to -7 decibels (dB) in at least one eye. Eyes meeting this criteria will be defined as 'study eyes'
7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses, (reliability confirmed by the Visual Field Reading Centre) in study eyes
8. Two or more headache days over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period
9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.8, Appendix 8 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Able to provide written informed consent

    Note: This would restrict the ability of vulnerable patients, such as inmates of psychiatric wards, prison or state institutions, with commitment to an institution or a patient who is detained or committed to an institution by a law court or by legal authorities to be included on the grounds that informed consent could not be assumed.

5.2.2. Exclusion Criteria

Patients will not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusion criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth or seventh nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
6. 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

Vision related exclusion criteria:

7. Any disease other than refractive error that causes visual loss in the study eyes. Where there is uncertainly this would be determined by the Independent Adjudication Committee [IAC]
8. Refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in study eyes. In addition, participants with myopia of worse than -6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes. Where there is uncertainly this would be evaluated by the Independent Adjudication Committee [IAC]

Headache related exclusion criteria:

10. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

11. Untreated previously diagnosed obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
12. Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
13. COVID-19 vaccine within 2 weeks prior to screening
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which may affect the safety of the patient
16. History of drug-induced immune-mediated thrombocytopenia from exenatide products
17. Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
18. Using any glucose-lowering medication
19. Currently taking warfarin
20. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)
21. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
22. Any of the following abnormalities in clinical laboratory tests at screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
23. Using recreational or illicit drugs at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
24. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period

25. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
26. Any contraindication to lumbar puncture procedure in the opinion of the investigator
27. Has participated in any other interventional trial within 1 month prior to the screening visit.
28. Is pregnant or breastfeeding

Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2

6. TRIAL ASSESSMENTS AND PROCEDURES

6.1. Procedures at Each Visit

Trial procedures and timings are presented in the Time and Events Table, Table 1.

No procedures should be performed prior to obtaining informed consent. All visits (except telephone call visits) should be performed at the clinic. Should a clinic visit not be possible, due to a patient self-isolating, the visit will be conducted at the earliest opportunity and will not constitute a protocol deviation.

6.1.1. Visit 1 Screening

The screening period must be a minimum of 7 days, up to a maximum of 10 days. Visit procedures can be performed in a single visit or over a number of visits during the screening period. Ideally all screening procedures should be performed on the same day.

- Obtain patient's written informed consent
- Eligibility criteria
    - Including confirmation that diagnostic LP occurred within the last 4 weeks with an opening pressure ≥ 25 cm CSF in lateral decubitus position
- Demographics (sex, age and ethnicity)
- Medical and ophthalmic history
- Concomitant mediation history
- Headache history (including family history of migraine (a first degree relative with and migraine) and headache in the 7 days prior to diagnostic LP)
- Headache preventative medication review
- Headache diary dispensed and diary training – to be performed on first day of screening.
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Height, body weight and BMI
- Full physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram

- Visual Assessments to both eyes
    - Frisén grading will be initially assessed by the site and then the presence of papilloedema verified by the OCT Reading Centre. Where there is uncertainty, fundus photos and or ultrasound scan (B scan) of the optic nerve may be conducted for evaluation by the IAC to confirm eligibility.
    - Optical coherence tomography imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard using a size III white stimulus)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay, and where there is uncertainty about eligibility this should be referred to the IAC.
    - Visual Acuity (LogMAR score)
- Laboratory assessments
- Trial medication training. Patients will be asked to self-administer 1 dose of placebo at the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable will be excluded

6.1.2. Visit 2 Baseline

- Review eligibility criteria
- Concomitant medications review
- Headache preventative medication review

- Review headache diary (Patient must meet required number of headache days as per inclusion criteria. If the headache diary exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit)
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse events review
- Targeted physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Visual Assessments to both eyes
    - Frisén grading will be assessed by the site
    - Optical coherence tomography imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
    - Visual Acuity (LogMAR score)
- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form

- Laboratory assessments
- Anti-Drug Antibodies (ADA) blood sampling
- Patient randomised
- Trial medication training
- Trial medication dispensed and first dose self-administered at clinic. This is a drug with a known tolerability and safety profile and hence there is so specific requirement on the duration of observation after injection. Subjects can be discharged from the site at the investigator's discretion. Patients will then be instructed to administer subsequent doses once weekly.
- Pharmacokinetic sampling (post-dose)

6.1.3. Visit 3 Telephone call

All patients will receive a telephone call at visit 3 to conduct headache preventative medication review, check for any AEs or changes in medication, procedures outside of protocol, health utilisation, to remind them to complete their diary and to answer any questions they may have on administration or storage of the trial medication.

6.1.4. Visits 4, 5, 6, 7, 8 and 9 Clinic visits

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI (not visit 4)
- Adverse event review
- Targeted physical examination (visit 6, 8 and 9 only)
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging

- Sites should initially check the scan quality. The OCT scan should then go through the upload processes to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.

- Humphrey Visual Field (24-2 SITA-Standard)
  - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
- Visual Acuity (LogMAR score)

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary (not visit 4)
- Health Utilisation Form
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-Drug Antibodies blood sampling
- Trial medication dispensing (not Visit 4) and accountability - patients should be reminded by the trial site to self-administer the trial medication weekly and to return used and unused trial medication at clinic visits

6.1.5. Visit 10

In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.

Where more than one dose has been missed during the 4 weeks preceding visit 10, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day

intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days.

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse event review
- Targeted physical examination
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
    - Visual Acuity (LogMAR score)
- Lumbar puncture (within 7 days of last dose of trial medication)

- Lumbar puncture to be performed ideally after visual assessments
- Performed in the lateral decubitus position according to LP SOP Appendix 1
- In some cases the lumbar puncture might be conducted using imaging guidance according to the preference of the individual and site. This could be using x-rays, computer tomography or ultrasound guidance.
- If the procedure is not successfully performed it should be re-booked and repeated as soon as possible and the patient should remain on trial medication with the last dose within 7 days of the LP.

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Patient global impression of change question
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-drug antibodies blood sampling
- Trial medication accountability

Where it is not feasible to conduct all of visit 10 procedures on the same day, these could be split provided visual assessments are performed before the LP and the patient remains on trial medication with the last dose within 7 days of the LP.

6.1.6. Visit 11 Follow-Up

This visit will be performed as a telephone call to conduct headache preventative medication review and check for any AEs or changes in medication. In the event of any abnormal safety assessments identified at the end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments.

A urine pregnancy test (for women of childbearing potential) will be performed, this can be conducted at home if the visit is performed by telephone call.

6.1.7. Unscheduled visit for repeat visual assessments

Optional unscheduled visit for visual testing (HVF, OCT, LogMAR) for patients where there is concern about their visual decline or who perform inadequately or where there is

technical failure (more than 15% false positive responses or inadequate performance indicated by the Visual Field Reading Centre for HVF; or OCT imaging not of satisfactory quality as determined by the OCT Reading Centre). Imaging only in the study eye(s).

- Optical coherence tomography Imaging
  - Sites should initially check the scan quality. The OCT scan should go through the upload process to the OCT Reading Centre. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
- Humphrey Visual Field (24-2 SITA-Standard)
  - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. Quality reports from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
- Visual Acuity (LogMAR score)

6.2. Trial Procedures

6.2.1. Screening Procedures

6.2.1.1. Demographics

The Investigator, or designee, should record the patient's sex, ethnicity, age, height, body weight and BMI at screening.

Ethnicity data will be collected in order to monitor any response differences in IIH disease progression/symptoms in different ethnicities.

6.2.1.2. Medical, Headache and Ophthalmic History

The Investigator, or designee, should record any ongoing co-morbidities and significant medical, headache and ophthalmic history along with the year in which such co-morbidities began (where known).

6.2.1.3. Reporting of Prior and Concomitant Medication

Concomitant treatment is any medication or therapeutic intervention being continued by the patient at trial entry and any new medication received during the trial. Prior treatment includes previous medications, treatments and interventions received in the past but no longer ongoing.

For this trial, only relevant prior concomitant medications within the last 4 months will be recorded. These include:

- Treatment to lower ICP (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
- Headache preventative medication (including oral or botulism toxin A or monoclonal antibodies against CGRP or CGRP antagonists, or greater occipital nerve block)
- GLP-1 receptor agonist
- Warfarin
- Glucose lowering medication
- Recreational or illicit drugs

At every visit the Investigator or a qualified designee will ask the patient about relevant concomitant medication.

No new medication should be started during the trial, unless medically necessary. The patient should be advised to consult the Investigator or designee before taking any prescribed or over-the-counter medications. In the case of headache preventative medications or ICP lowering medications please see details in the rescue therapy section. Acute headache analgesics are permitted and should be reported in the diary.

6.2.2. Safety Procedures

6.2.2.1. Physical Examination

A full physical examination will be performed at the screening visit. At a minimum the following will be assessed: ear, nose and throat, cardiovascular system, pulmonary system, skin, abdomen and neurological system. At all other time points a targeted (symptom directed) examination will be performed at the Investigator's discretion.

6.2.2.2. Twelve- Lead Electrocardiogram

Twelve lead ECGs should be performed at the times outlined in the Time and Events table (Table 1) in a standardized manner, i.e., after the patient has rested in the semi-supine position for at least 10 minutes. Measurements will be made using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, and QT intervals.

All ECG traces will be reviewed and signed by the Investigator or designee and any abnormalities will be marked as clinically significant or not clinically significant.

6.2.2.3. Vital Signs

Vital signs, including systolic and diastolic blood pressure and heart rate, will be measured at the time points specified in Table 1.

Patients should rest in a supine position for 10 minutes before the vital signs are assessed. Three recordings will be taken and averaged.

6.2.2.4. Laboratory Assessments

Blood and urine samples will be processed at the site. Routine biochemistry and haematology samples will be evaluated at the trial appointed central laboratory. PK, ADA and CSF samples will be stored at the central laboratory and evaluated at a qualified international laboratory. Details of handling and shipping are described in the Laboratory Manual.

6.2.2.4.1. Haematology

Blood for the assessment of haematology parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Total blood count; consisting of:

- Red blood cells
- Haematocrit
- Mean cell volume
- Mean cell haemoglobin
- Mean cell haemoglobin concentration
- Glycated haemoglobin (HbA1C)
- Blood glucose (non-fasting)
- Platelets
- White blood cells
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Coagulation (prothrombin time, international normalised ratio, activated partial thromboplastin time, thrombin time, fibrinogen)
- Basophils

6.2.2.4.2. Clinical Chemistry

Blood for the assessment of clinical chemistry parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen
- Creatinine
- Total bilirubin
- Total protein

- Albumin
- Alanine transaminase
- Aspartate aminotransferase
- Alkaline phosphatase

6.2.2.4.3. Urinalysis

Urine samples will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed at each time point:

- Glucose
- Ketones
- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen

6.2.2.4.4. CSF

CSF sample from visit 10 LP will be retained for future potential analysis of disease and drug related biomarkers.

6.2.2.4.5. Pregnancy

At screening blood will be collected to enable a serum pregnancy test to be performed. At visits thereafter, urine will be collected from female patients of childbearing potential at the times outlined in the Time and Events table (Table 1) to enable highly sensitive urine-based pregnancy tests to be performed. Female patients who are identified as being pregnant during the trial will be withdrawn from further treatment but will continue to attend safety follow-up visits.

The Investigator or designee should report any pregnancies in female patients to the Sponsor or designee, using the Pregnancy Report Form, within 24 hours. The contact details for reporting are:

[redacted]

Female patients or partners of patients who become pregnant should be followed until delivery, stillbirth or termination. The outcome of the pregnancy and, if applicable, the health of the baby, should be reported to the Sponsor using the Pregnancy Report Form.

6.2.2.4.6. Pharmacokinetic sampling

Pharmacokinetic sampling is to characterize the pharmacokinetics of exenatide after once weekly subcutaneous administration of Presendin at the times outlined in the Time and Events table (Table 1).

The primary purpose of the pharmacokinetic sampling is to characterize the steady state concentrations of exenatide. All actual sampling times and dosing times will be recorded.

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.4.7. Anti-drug Antibodies sampling

Anti-drug antibodies sampling will be performed in all subjects at the times outlined in the Time and Events table (Table 1).

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.5. Adverse Events

Patients will be asked non-leading questions to assess how they are feeling at each clinic visit. Adverse events will be assessed and reported as outlined in Section 12.

6.3. Efficacy Procedures

6.3.1. Intracranial Pressure

Assessment of ICP will be measured by LP in the lateral decubitus position. The diagnostic LP is performed by the clinical team prior to recruitment and the measurement must be made from the lateral decubitus position. The research LP will be performed according to LP standard operating procedure (SOP), Appendix 1. Lumbar puncture will ideally be performed after visual assessments as outlined in the Time and Events table (Table 1).

In some cases the lumbar puncture might be conducted using imaging guidance according to the preference of the individual and site. This could be using x-rays, computer tomography or ultrasound guidance.

Any additional LP procedures, outside of the protocol would constitute a protocol deviation and ideally should be discussed with the Investigator before the procedure is performed.

Non-protocol LPs should be recorded in the Case Report Form.

6.3.2. Visual Assessments

Visual assessments should be performed on both eyes. All visual assessments should be uploaded without delay on the day of the visit to the OCT and Visual Field Reading Centres. In all cases the site is responsible for initial checks of the clinical data in the wider context of the patient's disease, as well as a data quality check.

6.3.2.1. Frisén grade

At Screening (visit 1) Frisén grading (0 – 5) should initially be performed at the site through a dilated pupil. The presence of papilloedema will be verified by the OCT Reading Centre at screening (visit 1) and a report sent to the site. During screening, where there is uncertainty regarding the presence of papilloedema and / or Frisén grade a fundus photo and or ultrasound scan (B scan) of the optic nerve may be conducted (or may be requested by the OCT Reading Centre) and if uncertainty persists evaluated by the IAC.

At Baseline (visit 2) sites will reconfirm the Frisén grade

6.3.2.2. Optical Coherence Tomography

Imaging may be acquired using Heidelberg Engineering or Cirrus platforms according to the OCT SOP. Key measures are RNFL, optic nerve head size, and macular ganglion cell layer/complex thickness..

- Sites should initially check the clinical interpretation of the OCT scan and scan quality. The OCT should then go through the upload processes to the OCT Reading Centre. The OCT will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will then be sent to the site. Where the OCT is of insufficient quality, it should be repeated as soon as possible. Where the OCT has not been processed correctly at the site the processing should be re-performed as soon as possible thereafter. Repeated or reprocessed images would then be again transmitted to the OCT Reading Centre for a full assessment.
- If the site is concerned with the OCT findings, suggesting that the patient is a potential treatment failure and may require rescue therapy, the OCT Reading Centre review will be prioritised and when indicated expedited to the IAC.

6.3.2.3. Humphrey Visual Field

The visual field will be measured by Humphrey Visual Field analysis (24-2 SITA-Standard) including standardised refraction as indicated, according to the Visual Field Centre SOP (Manual of Procedures).

- At screening HVF will be reviewed by the Visual Field Reading Centre to confirm eligibility.
- Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in study eyes (including >15% false positives), is an exclusion criterion. HVF can be repeated to obtain as assessment with reliable performance.
- If the site is concerned with the HVF findings, suggesting that the patient is a treatment failure and may require rescue therapy, the Visual Field Reading Centre review will be prioritised and when indicated expedited to the IAC.

6.3.2.4. Visual Acuity

Assessment of visual acuity will be recorded using a LogMAR chart (unaided, best corrected, and with pin hole).

6.3.3. Headache Assessments

Patients will be provided with an electronic/paper diary at screening to complete during the trial. Information collected will be used to assess the following headache parameters:

- Monthly headache days
- Monthly moderate to severe headache days
- Responder rate
- Monthly acute analgesic use
- Headache severity (11-point NRS)

6.3.3.1. Headache Preventative Medication Review

A review of any headache preventative medications taken by the patient will be undertaken at each clinic visit. If the Investigator alters the headache preventative medication, this will be considered rescue medication (Section 10.1.1) and the IAC consulted. Use of headache preventative medication will be recorded at trial visits as outlined in the Time and Events table (Table 1).

Patients will record their acute headache analgesic use in their trial diary.

6.3.4. Patient Reported Outcomes

6.3.4.1. Visual related

Assessment of visual related quality of life will be derived from self-reported responses to the VFQ-25-10 item supp (see Section 16.6 Appendix 6).

6.3.4.2. Health-related

Assessment of health-related quality of life will be derived from self-reported responses using the following questionnaires:

- 36-item short form survey
- EuroQol -5 dimension -5 level survey

A Healthcare Utilisation Form will be completed by the trial site staff at clinic visits.

All questionnaires can be found in Section 16, Appendix 3 for SF-36 and Appendix 4 for the EuroQoL- 5D-5L survey.

6.3.4.3. Headache related Quality of Life

Assessment of headache-related quality of life will be derived from self-reported responses to the Headache Impact Test-6 questionnaire and performed at time points as outlined in the Time and Events table (Table 1). A copy of this questionnaire can be found in Section 16.5, Appendix 5.

6.3.4.4. Patient Global Impression of Change

The Patient Global Impression of Change will be conducted at visit 10, as outlined in the Time and Events table (Table 1).

It is a single item questionnaire using a seven-point verbal response scale to assess overall change in the patient's status since taking trial medication. A copy of this questionnaire can be found in Section 16.7, Appendix 7

6.3.5. Body Weight and Body Mass Index

The patient's body weight and BMI will be measured at the time points as outlined in the Time and Events table (Table 1).

The patient's height will be measured at Screening (shoes off).

7. SAFETY MEASURES DUE TO A GLOBAL CRISIS

The COVID-19 global pandemic presents numerous challenges to the conduct of ongoing clinical trials. In line with the FDA and European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (EMA, 2021), the following protocol considerations are provided to ensure patients safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic (or other global crisis) on this clinical study, additional details will be added to respective study manuals, project plan documents, and communicated to the investigative sites as needed. For any additional questions, the investigator should confer with the sponsor.

Number of Trial Patients

The evolving situation of the pandemic (or other global crisis) may result in a substantial number of patients' early withdrawal from the study, which could affect the data integrity of the study. Because of this risk, the sponsor may decide to recruit additional patients in the study, beyond the expected number, to mitigate such risk.

Study Visits

There are a number of on-site visits that would be required to ensure study validity. If there are local travel restrictions, isolation requirements, or the investigator determines it to be unsafe for patients to attend their scheduled study visits, the site staff may conduct certain visits via telemedicine (phone or video calls) to minimize patient risk as follows.

Screening Period

The following visit must be performed in person:

- Screening/Visit 1
  Note: To minimize direct, in-person contact between site personnel and patients, certain screening procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site.
  Specifically, the following procedures may be done remotely:
  - Informed consent (where applicable, per approved IRB/IEC process)
  - Demography
  - Medical and ophthalmic history
  - Concomitant medication history

- Headache history
- Headache preventative medication review
- Train and dispense headache diary
- Trial medication training

Randomised period

- Baseline (Visit 2)
  There are essential aspects to the baseline visit which must be performed in person.
  If the baseline visit is delayed the headache diary should utilise the preceding 7 days data. Where the visit is delayed by more than 10 days due to a global crisis the patient will be considered to have failed screening. Patients who screen failed due to the pandemic (or other global crisis) may be rescreened at a later time, if feasible.

  To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:
  - Concomitant medication review
  - Headache preventative medication review
  - Headache diary review
  - Adverse events
  - Patient reported outcomes
  - Health utilisation form

- Visit 4, 5, 6, 7, and 8
  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination
  - Urine pregnancy test

- Electrocardiogram
- Optical coherence tomography imaging
- Humphrey Visual Field
- Visual acuity testing
- Laboratory assessments
- Pharmacokinetic sampling
- Anti-drug antibodies sampling

To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Adverse events
- Patient reported outcomes
- Health utilisation form

- Visit 10

  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination
  - Urine pregnancy test
  - Electrocardiogram
  - Optical coherence tomography imaging
  - Humphrey Visual Field
  - Visual acuity testing
  - Laboratory assessments
  - Pharmacokinetic sampling
  - Anti-drug antibodies sampling
  - Lumbar puncture*

* Lumbar puncture to be ideally performed after visual assessments. In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days, if possible, but this can be extended according to local government policy if a patient is unable to attend (for example if a patient is self-isolating) as long as medication use is maintained as above.

- Follow up/ Visit 11
  This should be performed as a telephone visit unless clinical contact is necessary, as per protocol. Where face to face contact is required, this should be conducted at the earliest available opportunity.

Study Drug Dispensation and Distribution

If a patient is not able to attend a clinic visit, to ensure the continuity of providing patients' study drug within the constraints imposed by the pandemic (or other global crisis), the site staff may decide to supply study drug to patient as follows:

- Adequate supplies of study drug can be shipped to the patient by the study staff using a third-party service with approval from the patient. The third-party vendor will be agreed upon with the sponsor.
- The patient may request, with prior arrangement/agreement with the site, an authorized individual (a relative or delegate) to retrieve the study drug from the study site if the patient is unable to personally to do so.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (e.g., phone calls, emails, video visits) with the sites to get information on study progress, patient

status, and information on issue resolution as detailed in the Data Monitoring Guidelines, Remote source data verification.

If the trial site monitor cannot be on-site to carry out the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be carried out by a pharmacist from the site pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the site pharmacy directly, or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts with Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of patient for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

Clinic visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as the crisis-related limitations permit.

All safety data that are possible to obtain locally should be collected at a remote visit. These measurements may include the use of local practitioners and resources.

Exceptional measures taken in response to a crisis (e.g., COVID-19) and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3 guidance.

8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

Patients will receive lifestyle advice as per routine care from their treating physician.

9. INVESTIGATIONAL PRODUCT

9.1. Dosage and Administration

9.1.1. Randomised Period

During the 24-week randomised treatment period (Figure 1) patients will be randomised in a 1:1 ratio to receive active treatment or placebo.

Either

Presendin (2.0mg exenatide) as a SC injection, self-administered once weekly.

Presendin is supplied as 2 parts, one vial consisting of a drug part (white or grayish white powder in a clear vial) and one pre-filled syringe containing the diluent part (colourless liquid). The drug part is suspended in the diluent part solution and administered as a suspension.

or

Placebo as a SC injection, self-administered once weekly.

Placebo is supplied as 2 parts (visually identical to the Presendin vial and pre-filled diluent syringe). The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. The drug part is suspended in the diluent part solution and administered as a suspension.

9.2. Dose Rationale

The proposed 2mg weekly dose was based on the pharmacokinetic performance of the Peptron formulation (PT320). Pharmacokinetic profiles obtained after repeated once weekly dosing of 2mg of PT320 s.c. (as specified in the Presendin IB phase 2 clinical study in patients with type 2 diabetes) were comparable to those predicted by the population PK model developed for weekly s.c. administration of the recommended dose of the 2mg Bydureon extended-release formulation [Cirincione 2017],with time to reach the steady state slightly shorter for PT320 than for Bydureon (7-8 weeks vs 8-10 weeks) and with steady state plasma concentrations remaining within a comparable range for both products. Based on the same molecule and dose, comparable plasma concentrations for PT320 and Bydureon and the established safety profile of Bydureon a similarly acceptable safety and tolerability profile for PT320 is expected.

9.3. Maintaining the Blind

This is a double-blind trial.

A computer/website system will be used to maintain the blind for this trial. The site will be provided with website login details for the system. If the Investigator needs to unblind a patient's treatment, due to a medical emergency, the website should be accessed to unblind for that patient. .

The responsibility to break the treatment code in emergency situations resides solely with the investigator.

9.4. Treatment Assignment

Patients will be randomised in a ratio of 1:1 to receive active treatment (Presendin) or placebo. A computer/website system will be used to randomly assign each patient to a treatment arm.

9.5. Packaging and Labelling

Individual supplies of trial medication will be provided to the sites in a double-blind format. The labels will contain all information required to meet the applicable local regulatory requirements.

Further information on packaging, labelling and dispensing are included in the Pharmacy Manual.

9.6. Preparation

Each dose of trial medication is provided as two parts, a single use vial and a pre-filled syringe of diluent. Patients will receive training and be provided with an instruction sheet with details, on how to store, prepare, self-administer and discard/keep used trial medication.

9.7. Handling and Storage

Presendin, the active trial medication, contains the active ingredient, exenatide, which is hygroscopic and light sensitive and must be protected from light during storage. Prior to use, all trial medication should be stored refrigerated at 2-8ºC.

9.8. Product Accountability and Assessment of Compliance

In accordance with International Council of Harmonisation – Good Clinical Practice (ICH-GCP), each trial centre will account for all supplies of trial medication. Details of receipt, storage, assembly, and return will be recorded. The unit of accountability will be one single active or placebo vial. Needles will be disposed of in a sharps box.

All unused supplies will either be destroyed or returned to the trial Sponsor at the end of the trial in accordance with instruction by the Sponsor.

All trial medication will be self-administered by the patients. If a dose is not administered as planned, patients will record the missed dose in their electronic/paper diaries and it will be documented in the electronic case report form (eCRF).

9.9. Treatment of Investigational Product Overdose

Definition of Overdose: More than 1 (one) dose in 24 hours.

In the event a patient overdoses on trial medication the Investigator should be notified as soon as possible. If symptoms appear, the Investigator will treat the patient according to their clinical judgement depending on the type of clinical signs and symptoms exhibited by the patient. The Sponsor should be notified in writing within 24 hours of the Investigator becoming aware.

Effects of overdose that may be seen include severe nausea, severe vomiting and rapidly declining blood glucose concentrations.

9.10. Occupational Safety

There are no known occupational safety risks to staff. The Material Safety Data Sheet will be made available where required by local regulations.

10. TREATMENT FAILURE AND RESCUE THERAPY PROCEDURES

10.1. Treatment Failure

Rescue therapy can be initiated when there is a treatment failure. Since perimetric variability increases with increasing visual field damage, a two-tiered approach is used [Wall, 2013].

10.1.1. Possible treatment failure

Possible treatment failure is defined as those with baseline PMD between -2 and -3.5dB who experience a decline of > or equal to 2dB. In those with a baseline PMD between -3.5 and -7 dB, those who experience a decline of > or equal to 3 dB.

When a possible treatment failure is identified, perimetry, and if needed, other visual tests, should be repeated at an unscheduled visit.

10.1.2. Definite treatment failure

A definite treatment failure occurs when a patient with baseline PMD between -2 and -3.5dB experiences a decline of > or equal to 2dB which remains after repeat perimetry.

Or in those with a baseline PMD between -3.5 and -7 dB who experience a decline of > or equal to 3 dB which remains after repeat perimetry.

These cases should be reviewed without delay by the IAC (who will review all visual and clinical data) to confirm or refute a definite treatment failure.

10.2. Rescue Therapy/Rescue Intervention for Progressive Visual Loss

When a treatment failure occurs, rescue therapy can be initiated, in addition to study treatment, based on the medical judgement of the Investigator. Decisions should always be discussed with the IAC without delay and if possible before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to be a medical emergency. In all cases the final decision lies with the Investigator.

Patients showing progressive visual loss will be considered for rescue therapy with acetazolamide or an alternative diuretic. In cases where the visual loss is severe and "rapid", and believed by the Investigator to necessitate surgical intervention, the intervention will be conducted in accordance with local emergency practice.

10.2.1. Rescue Therapy for Headache

If the Investigator wishes to alter the headache preventative medication (any drug can be considered), this decision should always be discussed with the IAC before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to be a medical emergency. Use of headache preventative medication will be recorded at trial visits.

Use of acute headache analgesics is not considered as rescue medication and is permitted but must be documented in the headache diary (monthly analgesic use).

11. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

11.1. Recording Prior and Concomitant Medication

All relevant medication taken within 4 months of screening should be recorded in the eCRF along with all relevant medication taken from the start of the screening period until the final follow-up visit (Section 6.2.1.3).

At a minimum the following information will be collected:

- Generic name
- Dose
- Frequency
- Date started
- If ongoing (or if not, then the date stopped will be recorded)
- Reason for taking the medication

11.2. Prohibited Medications

11.2.1. Prior to screening and randomisation

- Treatment to lower ICP within 1 week prior to screening (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed).
- Exposure to fluoroquinolones, lithium, vitamin A, or tetracyclines within 2 months of diagnostic LP
- Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
- Warfarin
- Glucose-lowering medicationCOVID-19 vaccine within 2 weeks prior to screening
- Recreational or illicit drugs during screening period

  Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2.

11.2.2. During the trial

- Treatment to lower ICP (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed). These will all be considered rescue medication (Section 10.1.2) and the IAC consulted. Use will be considered a protocol deviation.
- If the Investigator alters the headache preventative medication (including oral or botulism toxin A or monoclonal antibodies against CGRP or CGRP antagonists, or greater occipital nerve block) this will be considered headache rescue medication (Section 10.1.2) and the IAC consulted.
- Glucagon like peptide-1 receptor agonists
- Recreational or illicit drugs
- Warfarin
- Glucose-lowering medication
- Regarding COVID-19 vaccination, the risks of receiving or not receiving the vaccination have been considered in relation to the IMP and no additional risks are envisaged. Hence patients may choose to have or not have COVID-19 vaccination or booster during this trial.

The investigator should follow the cautions and guidance on the management of other concomitant medication or DDIs as detailed in section 9.2.5.2 (Drug-Drug Interactions) of the IB.

12. PATIENT COMPLETION AND WITHDRAWAL

12.1. Patient Completion

Patients will be classed as having completed the trial once they have completed all required trial visits. See Section 11.2.1 for early discontinuations.

12.2. Patient Withdrawal

12.2.1. Patient Withdrawal from Trial Treatment

A patient will be withdrawn from treatment for any of the following reasons:

- Withdrawal of consent to continue in the trial. The reason for this will be documented if provided
- The Investigator or Sponsor, for any reason, decides the patient should be withdrawn from the treatment
- Lack of compliance with the trial medication is classified as <75% or >125% of scheduled doses over the course of the trial, excluding supply issues
- Adverse events, which cannot be tolerated by the patient
- Pregnancy during the treatment period
- Retroactive failure to fulfil inclusion/ exclusion criteria (in this clinical drug trial designated phase III), if individual Benefit/Risk does not overrule
- New medical conditions not allowing for continuation of the protocol conform treatment
- Enrolment in any other clinical trial involving an investigational product, or enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study
- If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication
- If the patient, for any reason, requires treatment with a concomitant medication that during this trial should be avoided for reasons of safety and/or efficacy reasons
- Any code breaking/unblinding requested by the investigator
- Protocol-mandated permanent discontinuation of the investigational study treatment

Patients will be encouraged to continue in the trial to the end of the randomised treatment period even if they stop trial medication so that data can be collected for the Intention-To-Treat (ITT) population.

If a patient is withdrawn from treatment during the randomised treatment period, they will be encouraged to return for all trial visits up to visit 10. If a patient does not want to return then at a minimum they should be encouraged to attend for visit 11 procedures as a safety follow-up visit.

12.3. Treatment after the End of the Trial

Patients will not be provided with trial medication following the end of the trial.

12.4. Screen and Baseline Failures

Information will be collected on all patients who sign the Informed Consent Form (ICF).

13. ADVERSE EVENTS

13.1. Definitions

13.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

13.1.2. Adverse Drug Reactions

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

13.1.3. Serious Adverse Events or Serious Adverse Drug Reactions

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Deterioration of IIH necessitating CSF shunting or optic nerve sheath fenestration or dural venous sinus stenting will be recorded as an SAE and reported.

Deterioration of IIH necessitating hospital admission will be recorded as an SAE and reported.

Pre-defined exclusions:

- Hospitalisation for unrelated elective procedures
- Post LP headache

13.1.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to the trial medication and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator Brochure) and serious.

13.1.5. Expected Adverse Events

Perceived deterioration of IIH necessitating attendance or admission to hospital will not be reported as an SAE, but these events will be reported and recorded at follow-up. Non-protocol LPs will be reported at follow-up.

13.1.6. Adverse Events of Special Interest

There are no Adverse Events of Special Interest (AESIs).

13.2. Causal Relationship

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

- Probable relationship: event occurs in a plausible time relationship to the medication administration and cannot be explained by concurrent disease or other drugs or chemicals; the response to the withdrawal of the drug should be clinically plausible
- Possible relationship/ relationship cannot be ruled out: event occurs with a reasonable time sequence to the medication administration, but could also be explained by concurrent disease or other drugs or chemicals; information on the drug withdrawal may be lacking or unclear
- Unlikely relationship: event occurs with little temporal relationship to the medication administration and other factors such as drugs, chemicals or underlying disease provide plausible explanations
- Not related: event has no temporal relationship to the medication administration or there is a definite alternative aetiology

13.3. Severity Criteria

An assessment of severity grade will be made using the following categorical descriptors:

- Grade 1 means a relatively minor side effect
- Grade 2 means a moderate side-effect
- Grade 3 means a severe or medically significant but not immediately life-threatening side-effect
- Grade 4 means life-threatening consequences
- Grade 5 death related to AE

The exact definition of each number in the scale depends on the particular side effect according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [CTCAE].

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g., laboratory abnormalities).

Adverse events occurring as a result of LP should be specifically recorded. Occurrence of post lumbar headache will be specifically reported.

13.4. Reporting Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's final safety follow-up visit. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol. Adverse events reported after dosing will be classed as treatment emergent AEs.

All AEs, regardless of seriousness, severity, or presumed relationship to trial therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the source documents and the eCRF their opinion concerning the relationship of the AE to trial therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.The patient must be provided, on the first day of trial medication (Day 1), with a "patient card" indicating the following:

- Patient number
- Name of the investigational product
- Investigator's name and 24-hour contact information
- Statement that the patient is participating in a clinical trial

13.4.1. Reporting Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor designee (contract research organisation) immediately without undue delay of the investigator becoming aware of the event.

SAEs will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's final safety follow-up visit.

However, the investigator must immediately notify the sponsor if, after completion of the clinical trial, he/she becomes aware of a serious adverse event in a subject suspected of being causally related to the investigational product.

Information regarding SAEs will be transmitted to the Sponsor's safety contact using the SAE Form, which must be completed and signed by the Investigator, and transmitted to the Sponsor's safety contact immediately without undue delay.

The contact details are:

[redacted]

The Sponsor assumes responsibility for appropriate reporting of SAEs or SUSARs to the regulatory authorities. The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee (IEC) that approved the protocol unless otherwise required and documented by the IEC.

An annual safety report will be submitted to the Institutional Review Board once a year via the Investigator.

13.5. Reporting and Handling of Pregnancies

Pregnant patients will be withdrawn from the trial.

Female patients will be instructed to notify the Investigator immediately if they become pregnant during the trial and up to 12 weeks after discontinuation/completion of trial medication. Pregnant patients will be withdrawn from further trial treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the trial.

A pregnancy as such is not an AE, unless there is a possibility that the trial medication has interfered with the efficiency of any contraceptive measures. The Investigator should report all pregnancies to the Sponsor contact or designee within 24 hours of being informed of them. The pregnancy report form should be used instead of the SAE form.

The pregnant patients will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

Patients will give consent on enrolment that the Investigator will report any pregnancy to the Sponsor and that further information will be collected until delivery.

14. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalised prior to database lock providing detailed methods for the analyses outlined below.

14.1. Hypotheses

This trial compares outcomes in IIH patients under Presendin and matched placebo. The primary hypothesis that will be tested is:

- The ICP measurement in the Presendin group is equal to the ICP measurement in the placebo group at Week 24; against the alternative that the outcomes differ

14.2. Trial Design Considerations

14.2.1. Sample Size Assumptions

The target sample size for the trial is 240 randomised patients, i.e., 120 patients per arm. We justify this figure in the following sections. The two outcomes for which we sought to power the study are ICP and PMD.

14.2.1.1. Intracranial Pressure Power

The most difficult parameters to specify for a sample size calculation pertain to the variability of outcomes. We present a brief summary of the literature. Baseline standard deviations (SD) of ICP in previous trials were: 5.4 (n=10) and 6.3 (n=17) in the Drug Trial [Markey, 2017]; 5.0 (n=16) (data on file); and 5.7 (n=32) and 5.3 (n=30) in the Weight Trial [Ottridge, 2017]. Post-baseline standard deviations were slightly lower (and less than 6.0) in three of these five arms; and increased slightly in one (but remained less than 6.0). The post-baseline standard deviation however increased to over 8.0 in the surgery arm of the Weight Trial because the surgical intervention dramatically impacted ICP in some patients. In the NORDIC trial [Wall, 2014] however, the standard deviation of baseline ICP was much higher, at 9.4 in the treatment arm (n=86). Seeking to avoid underpowering the study, we elected to proceed with the SD estimate for the NORDIC trial as this is the most similar trial population to the planned IIH EVOLVE trial (both recruiting acute IIH). We assume that control arm baseline and 24-week ICP SD equals 9.4, Presendin baseline ICP SD equals 9.4, and Presendin 24-week ICP SD equals 10.4. These values assume the variability of ICP measures in untreated patients is as high as has been seen in the NORDIC trial and assumes that the variability in treated patients is slightly higher still. We anticipate that the standard deviation will be slightly higher in the experimental arm as treatment effects will potentially manifest changes in ICP. However, we do not expect such variability to be as inflated in this trial relative to control as it was

in the Weight Trial because of the likely difference in treatment effect between surgical and drug interventions.

Under this parameterisation, when testing for a difference between arms at 24-weeks of 5 CSF (justified below) using a total sample size of 240, assuming that up to 50% of observations are missing (i.e. 60 final LPs are completed in each arm), using a 5% significance level by Analysis of Covariance (ANCOVA) adjusted for baseline ICP, the two stratification variables, and treatment arm, we expect to have approximately 85% power. If 40% of observations are missing (i.e. 72 final LPs are completed in each arm), we expect power to be 91%. These figures have been inferred by computer simulation. Of the 165 patients in IIHTT [Wall, 2014] it was reported that "only 85 participants (47 [55%] in the [treated] group and 38 [48%] in the placebo group) agreed to a lumbar puncture at month 6."

We expect a high rate of missing data because lumbar puncture is an invasive procedure that patients can find painful and traumatising [Scotton, 2018]. If patients have an unpleasant experience at the diagnostic LP they are also more likely to decline the LP at trial outcome. If patients do decline the final LP, logically it will be because of the baseline experience rather than their prevailing ICP. If data for the LP at 24 weeks is missing, the reason will be recorded.

Outcomes from previous trials show that baseline and post-baseline distributions of ICP show central tendency with approximate symmetry, so we conclude that normality is a reasonable assumption and therefore ANCOVA is a defensible analysis method.

14.2.1.1. Perimetric Mean Deviation Power

We summarise here the estimated power for detecting differences between arms in the PMD outcome measure. In the NORDIC trial [Wall, 2014], the authors observed that the improvement from baseline to 6-months in PMD was 0.71dB greater in the experimental arm than the control arm. Cross-sectional SD of PMD was 1.1-1.2 at baseline. Table 2 in their publication shows that the standard error of mean PMD is higher at 6m than at baseline, likely reflecting a combined effect of missing data at 6-months and greater variability of post-baseline measures. We plan to take repeated measures of PMD at baseline, 2 weeks, 1-month (m), 2m, 3 m, 4m, 5m and 6m. Assuming that the overall SD of PMD scores is 1.8, thus introducing some reasonable inflation on Wall *et al*.'s baseline variability parameter for the reasons identified, using the formula given on p.31 of Diggle, Liang & Zeger (1994) we would expect to require 142 patients in total to detect a difference of 0.71dB (justified below) with 90% power at a 5% significance level, if the serial correlation between repeated measures is 0.4 (and we expect a value in this region) [Diggle, 1994]. If the serial correlation parameter is as low as 0.3, the required sample size increases to 166.

Note that the method used above assumes full follow-up and data collection. Although every effort will be made to collect all outcomes, naturally some missing data is expected. If we inflate the maximum sample size identified above by up to 30% to account for some data loss, we require up to 166 / 0.7 = 237 patients. The assumed 30% missing data rate was adjudged to be realistic by the Sponsor based on previous trials in IIH. Thus, we expect to be able to cover the impact of missing data using the extra patients necessitated by the sample size calculation for ICP.

The above assumes only one eye is measured per patient. In actuality, some patients may provide outcomes for both eyes because any eye that satisfies the eligibility criteria (see Section 5.2) will be enlisted in the study. Put another way, all patients will provide outcomes in at least one eye, and some will provide outcomes in two. Second eyes will naturally be highly correlated with first eyes. From a sample size perspective, this means the additional information in second eyes will be of modest value. Nevertheless, outcomes on second eyes will contain some additional information and should be included in the analysis in the interest of efficiency. When estimating sample size, for the sake of simplicity and because of uncertainty in the rate of eligibility in second eyes, we have assumed that each patient yields outcomes from only one eye. Eligible second eyes will be included in the analysis with appropriate model terms to handle the within-patient correlation (further details are included in the SAP). As such we expect outcomes from second eyes to provide a modest uplift in power to the scenarios presented here.

This section assumes a longitudinal analysis method such as hierarchical regression.

14.2.2. Stratification

At the outset, it is expected that markers of disease severity will be prognostic of potential efficacy. For this reason, it is proposed to stratify randomisation by, baseline ICP (<35cm or ≥35 cm), baseline body mass index (< 30 kg/m^2 or ≥30 kg/m^2) and baseline PMD (worse than or equal to -3.5dB or better than -3.5dB).

14.2.3. Sample Size Sensitivity

14.2.3.1. Clinically Meaningful Effect Sizes

Minimally relevant effect sizes have not been fully determined in IIH given it is a rare disease with relatively few previous trials.

The ICP diagnostic threshold in IIH is 25 cm CSF [Mollan, 2018]. However, it is not necessary to reduce ICP <25 cm CSF to achieve remission from signs and symptoms of IIH in all patients [Sinclair, 2010]. The clinical importance of a particular change in ICP will vary depending on the starting ICP and the impact this pressure has on vision and

headache. Changes in ICP of 5 cm CSF are generally considered meaningful when treating IIH patients. For example, in a clinical study evaluating the benefits of weight loss in IIH patients, a 16.5% (6.2 cm CSF) reduction in ICP resulted in a statistically significant improvement in headache and vision measures as well as quality of life [Sinclair, 2010]. In the IIH Treatment trail (n=165), a study evaluating the drug treatment acetazolamide against placebo, a reduction of -5.9 cm CSF was seen in association with significant improvement in PMD, OCT measures of papilloedema and quality of life measures [Wall, 2014].

The minimally clinically important change in the perimetric mean deviation adopted into clinical practice was stablished by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) group and the IIH Treatment Trial (IIHTT). The investigators found a 0.71dB difference in the PMD between the two trial arms (comparing acetazolamide with placebo) that was clinically meaningful. The change of 0.71dB was interpreted as clinically meaningful as this was accompanied by significant changes in LP opening pressure, papilloedema (measured by OCT), general quality of life and visual related quality of life [Wall, 2014, Bruce, 2016].

The clinically meaningful effect size for MHD reflects that for a phenotypically similar headache, chronic migraine. Recent randomised trials in patients with chronic migraine [Tepper, 2017; Silberstein, 2017], episodic migraine [Goadsby, 2017], or both [Camporeale, 2018] have shown in post-baseline months 1–3, odds of migraine relative to baseline of 0.5–0.8 with placebo and 0.5–0.3 with experimental drugs. Decreases in MHD relative to baseline grew in time, and placebo responses were stronger in chronic migraine than episodic migraine. In the three placebo-controlled, blinded trials, these equated to odds-ratios of migraine compared with placebo of 0.8–0.6, or absolute differences of 1.5–2.5 MHD [Sinclair, 2010; Tepper 2017; Silberstein, 2017; Goadsby, 2017].

14.2.4. Trial Stopping Criteria

There are no trial-specific stopping rules.

The following events, if applicable, may cause premature termination of the clinical study or study arms:

- unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by sponsor or representative), e.g. when adverse events occur, unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile (substantial changes in risk-benefit considerations), and therefore medical and/or ethical reasons affect the continued performance of the study;

- new scientific evidence becomes available during the study that could affect the patient's safety (benefit-risk analysis no longer positive), e.g. new insights from other clinical trials;
- request of the sponsor with or without recommendation from the data safety monitoring committee, or of a regulatory agency, e.g. as a consequence of inspection;
- favourable opinion withdrawn by the ethics commission;
- in case of difficulties in the recruitment of the planned number of subjects in the indicated time (insufficient recruitment rate); -withdrawal of the license to manufacture and/or of the permission to import, it must either be adjusted or the clinical study/trial must be discontinued.

14.3. Data Analysis Considerations

14.3.1. Estimands

We have specified intercurrent events that are material to the measurement of our primary and secondary outcomes, and unbiased estimation of treatment effects attributable to Presendin.

ICP-lowering medication include: acetazolamide, topiramate, diuretics, glucocorticoids (oral dexamethasone and oral prednisolone). Headache-preventative medications include: amitriptyline, topiramate, nortriptyline, beta blockers, candesartan, sodium valproate, pizotifen, botox, CGRP-therapy.

14.3.1.1. Outcome: Intracranial pressure (ICP)

14.3.1.1.1. Intercurrent event: ICP-lowering medications

All patients are expected to have elevated ICP because it is a defining characteristic of the disease. ICP is a physiological variable that is unlikely to show spontaneous improvement without treatment. For these reasons, we expect ICP-lowering medication use to be greater in the placebo arm. If a patient takes medication that is intended to reduce their ICP, it is logical to expect that their ICP will be reduced. Outcomes from patients that take ICP-lowering medications will confound the estimation of the causal treatment effect of Presendin. We have no data to estimate the length of effects of ICP-lowering medications. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have used ICP-lowering medications and replace these observations with arm-specific imputations. This will allow estimation of the treatment effect that is

purely and causally attributable to Presendin. Patients will consent at enrolment to forgo the use of ICP-lowering medications and be informed that taking ICP-lowering medications during the trial would constitute rescue therapy and a treatment failure and be a protocol deviation.

14.3.1.1.2. Intercurrent event: Off-protocol lumbar punctures

Lumbar punctures are commonly conducted to reduce intracranial pressure [Weisberg, 1977; Johnston, 1981; De Simone, 2005]. In some centres, they are given routinely although this has now been advised against in the International IIH Guidelines (Soler, 1998; Mollan, 2018). As such, they remain a material therapeutic option. LP is expected to reduce ICP mean opening pressure 32 (28-37) cm CSF to 19 (17-21) cm CSF post LP [Yiangou, 2019]. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify change in ICP after an LP, it is expected that effects in the majority of change would have dissipated completely within two months [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have had an off-protocol LP within two months of the protocol-scheduled 24-week LP and replace these observations with arm-specific imputations. Where patients require off-protocol LP this would be a protocol deviation.

14.3.1.1.3. Inter-current event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in ICP [Sinclair, 2010]., Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure and replace with arm-specific imputations. Patients will be ineligible for the trial if they have had a surgical weight-loss procedure within 3 months of randomisation or fail to confirm that they do not intend to undertake such a procedure during the trial. They will also be informed at enrolment that undergoing a surgical weight-loss procedure would be a protocol deviation.

14.3.1.2. Outcome: Perimetric Mean Deviation (PMD)

14.3.1.2.1. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a

patient takes ICP-lowering medication (rescue medication due to treatment failure), it is logical to expect that their ICP will decrease and that papilloedema will reduce as a result, allowing visual fields to improve. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the PMD outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

14.3.1.2.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilloedema, allowing visual fields to improve. Patients that have LPs are expected to experience less pressure on the optic nerve, less papilloedema, and have better chances of their visual fields improving. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilloedema after an LP the consensus of clinicians would predict that effects of the LP on papilloedema and therefore visual fields would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. PMD outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove PMD outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

14.3.1.2.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including improvements in visual fields [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove PMD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

14.3.1.3. Outcome: Papilloedema measured by OCT (optic nerve head size, retinal nerve fibre layer)

14.3.1.3.1. Intercurrent event: ICP-lowering medications

All patients will suffer from papilloedema at enrolment as it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that the papilloedema will reduce in turn. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the OCT outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

14.3.1.3.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilloedema. Patients that have LPs are expected to experience less pressure on the optic nerve and therefore relatively less papilloedema. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilloedema after an LP the consensus of clinicians would predict that effects of the LP on papilloedema would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. OCT outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove OCT outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

14.3.1.3.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in papilloedema [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove OCT outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from

the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

14.3.1.4. Outcome: Monthly headache days (MHD)

14.3.1.4.1. Intercurrent event: Headache-preventative medications

The great majority of patients are expected to suffer from headache because it is a common symptom of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes medication that is intended to prevent headache, it is logical to expect that their headache burden will be decreased. Despite the widely-observed short-term placebo-effect observed in headache outcomes, we expect headache-preventative medication use to be greater in the placebo arm. Outcomes from patients that take headache-preventative medications will confound the estimation of the causal treatment effect of Presendin (more so with botulinum toxin A and CGRP therapies). For these reasons, we propose to remove the headache outcomes following the administration of headache-preventative medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin. Patients who require a change to their headache preventative medications will do this through consultation with the IAC and such a change would be regarded as headache rescue therapy.

14.3.1.4.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing the frequency and intensity of headache. Beneficial effects dissipate with time. Prospective data documents alterations in headache for at least 7 days and whilst there is no prospective longitudinal data over a longer time period consensus amongst clinicians would widely acknowledge that headache in some individuals can be influenced for up to a month [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. MHD outcomes will be recorded daily via diaries. For the reasons stated, we propose to remove MHD outcomes recorded in the 4-weeks following each off-protocol LP and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

14.3.1.4.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in headache frequency and severity [Sinclair, 2010].

Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove MHD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

14.3.1.4.4. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that headache will reduce as a result. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the MHD outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

14.3.1.5. Primary Estimand (Hypothetical assuming no concurrent procedures, irrespective of adherence to treatment)

The primary estimand is defined as the following for the primary endpoint:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect ICP.

The primary estimand for the initial secondary endpoint will be handled similarly to the primary endpoint using the “Hypothetical” approach. The initial secondary endpoint is defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect PMD.

14.3.1.6. Secondary Estimand (Hypothetical)

The secondary estimand for the primary endpoint is defined as follows:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect ICP.

The secondary estimand for the initial secondary endpoint will be defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect PMD.

All details will be defined in the SAP.

14.3.2. Analysis Populations

The following analysis populations are planned for this trial:

- **Safety Population:** The Safety population includes all patients randomised to treatment who receive at least one dose of trial medication. This will be the population used for all safety analyses unless otherwise specified.
- **Intent-To-Treat Population (ITT):** The ITT population includes all patients randomised to treatment. This will be the main population for all efficacy analyses unless otherwise specified.
- **Per Protocol (PP)**: The PP population includes all patients randomised to treatment without important non-evaluable protocol deviations. Only protocol deviations with the potential to affect the trial results significantly, or to invalidate the interpretation of the data obtained, will lead to exclusion of patients from the PP population. Protocol deviations to be considered will include (but will not be limited to):
    - Failure to meet inclusion/exclusion criteria
    - Wrong treatment or incorrect volume of drug administration
    - Prohibited concomitant medications
    - Compliance of less than 75% or>125% with trial drug administration

- Use of rescue procedures, including, off-protocol LPs, LP shunts or bariatric surgery

Assignment of patients to populations will be confirmed at a blinded data review meeting to be held before the trial database is locked.

If a patient is randomised incorrectly or is administered the incorrect trial medication, analyses of the ITT will be based on the assigned treatment, whereas all other analyses will be based on the actual treatment received.

14.3.3. Treatment Comparisons

Treatment comparisons will be undertaken between active and control groups. The primary outcome will be analysed as described in Section 13.2.1.

14.3.4. Safety Analyses

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, and ECG results.

All safety analyses will be performed on the Safety population.

14.3.4.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary (the most recent version before starting the trial will be used).

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

The number and percentage of patients reporting TEAEs, grouped by MedDRA system organ class and preferred term will be tabulated by treatment group. Summaries will be presented for all TEAEs, TEAEs by severity and TEAEs by relationship to trial medication.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged. The observation period in which an AE started will also be provided.

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed by trial arm. Treatment failures will be displayed by trial arm.

14.3.4.2. Clinical Laboratory Evaluations

Laboratory test results for each biochemistry and haematology parameter will be summarized descriptively by treatment group and time point as both observed values and change from baseline values.

The number of patients with clinical laboratory (biochemistry, haematology, and urinalysis) values categorized as below, within, or above the normal ranges (or as either normal or abnormal for urinalysis variables that do not have quantitative ranges), will be tabulated in relation to baseline (shift tables), for each clinical laboratory analyte by treatment group and time point.

Laboratory values will be displayed in the data listings and those that are outside the reference ranges will be flagged, along with corresponding normal ranges. Any patients with any markedly abnormal laboratory results will also be provided in a listing.

Pregnancy test results including reason, if not performed, will be listed.

14.3.4.3. Vital Signs and Body Mass Index Evaluations

Descriptive summaries of observed values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure and heart rate by treatment group and time point.

Body mass index will be derived at Screening, Baseline and Weeks 4, 8, 16, 24, 32 and 48 using height captured at Screening and weight at the respective assessment. Body mass index and weight will be summarized descriptively by treatment group and time point as both observed values and change from baseline values for Safety and ITT populations.

14.3.4.4. Electrocardiogram

Descriptive statistics of observed values and change from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected according to Fridericia's formula (QTcF). These summaries will be presented by treatment and time point for the Safety population.

The number and percentage of patients with values beyond clinically important limits will be summarised including those with an increase in QTcF >30 msec increase from baseline and >60 msec increase from baseline or those with an absolute QTcF value of >450 msec (male patients) or >470 msec (female patients).

14.3.4.1. Other Safety Evaluations

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed by trial arm.

14.3.5. Patient Reported Outcomes Analyses

All patient reported outcome endpoints (VFQ-25, HIT-6, SF-36, EQ-5D-5L) will be analysed as observed and presented with change from baseline in a descriptive summary of treatment and visit

The number and percentages of PGIC responses will be tabulated by treatment and visit.

14.3.6. Missing Data

Although every effort will be made to collect responses from all patients at all scheduled time points, there undoubtedly will be some missing data. The SAP describes in detail steps for dealing with missing data using relevant imputation strategies for specific endpoints that adjust for treatment arm, centre, baseline value, and stratification variables.

We briefly describe our imputation strategy for the analysis of primary and secondary efficacy endpoints here. Our imputation strategy generally applies for data being set to missing by having an intercurrent event or data that is not captured at all.

For the primary efficacy variable (lumbar puncture) there is only one post-baseline assessment planned at Week 24. In this case we will multiply impute missing values from the posterior predictive distribution of a generative regression model that will use explanatory variables:

- the randomisation stratification variables;
- treatment allocation;
- the baseline values of the outcome

Values for these variables must be established for all patients at baseline so we do not expect missing values here.

For outcomes with repeated measures (secondary efficacy variables), to the above list we will also add historic observations of the outcome in question, including imputed values. In chained equation models that seek to incrementally estimate repeated measures outwards from baseline, missing values are imputed for the first assessment time, then

values for the first assessment are included when imputing missing values for the second assessment time, etc.

The above multiple imputation models for both primary and secondary efficacy endpoints will be applied in a way that missing data will be imputed in different ways dependent on the reason for missingness. In case the data can be assumed to be missing at random (e.g. early discontinuation from study due to withdrawal of consent), the missing data will be imputed using the treatment arm to which the patient was randomised to. In case the data needs to be assumed to be missing not at random (e.g. early discontinuation due to adverse event), the missing data will be imputed to reflect outcomes in the placebo arm (e.g. for endpoints that are observed once, like ICP), or to reflect changes through time that are typical in the placebo arm (e.g. for repeated measures endpoints, like headache days). A detailed list of reasons for missingness and the corresponding way of imputation will be specified in the SAP. For the analysis of the secondary estimands, the same model will be used, but additional treatment events will be considered which require further imputations.

In both cases, the imputation process will finally be repeated several times to reflect the uncertainty in missing values. The analysis method described in this protocol will be performed on each complete imputed dataset. Final estimates of the treatment effect and its uncertainty will be derived by combining the analyses on the complete imputed datasets using standard methods, described in several sources including. (White et al, 2011).

For the analysis of the primary efficacy endpoint and for some of the important secondary endpoints, further sensitivity analyses for missing values will be planned to investigate the effect of missing values on the results, using simpler statistical models. For the primary efficacy endpoint this will include a completer analysis, as well as an analysis using baseline observation carried forward (BOCF), for the important secondary endpoints this will cover a mixed model for repeated measures (MMRM) model without replacing missing values, assuming that all missing values are missing at random as well as an analysis using last observation carried forward (LOCF). Details will be described in the SAP.

14.3.7. Reporting Deviations from the Statistical Plan

Any deviations from the planned analyses will be described and justified in the final clinical trial report.

15. TRIAL ADMINISTRATION

15.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Before initiation of a trial site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the trial in accordance with ICH-GCP and applicable country-specific regulatory requirements.

The trial will be conducted in accordance with all applicable regulatory requirements.

The trial will be conducted in accordance with the EU Clinical Trial Regulation 536/2014, ICH-GCP, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- An IEC/Institutional Review Board review and approval of trial protocol and any subsequent amendments and all ICFs or other information given to the patient
- Patient informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each patient before participation in the trial. Written informed consent will be collected following a review of the patient's information leaflet by the potential patient and a discussion between the patient and the Investigator or suitably qualified designee.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this trial. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site(s) by an outside authority before the Inspectors are permitted access to any of the trial records or the trial areas.

15.2. Trial Monitoring

In accordance with applicable regulations, ICH-GCP, the monitoring plan and the Sponsor's and/or delegate procedures, monitors will contact the site before the start of the trial to review with the site staff the protocol, trial requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data

collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The Sponsor and or delegated monitors will perform risk-based monitoring during the conduct of the trial to ensure that:

- The data are authentic, accurate and complete
- The patient's safety and rights are being protected
- The trial is conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP and all applicable regulatory requirements

15.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all relevant documents.

Information recorded in the eCRF should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory reports, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

15.2.2. Data Handling and Record Keeping

Following closure of the trial, the Investigator or head of the medical institution (where applicable) must maintain all site trial records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor SOPs and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

15.3. Provision of Trial Results and Information to Investigators

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical trial report. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete trial results at a mutually agreeable location.

The Sponsor will also provide the Investigator with the full summary of the trial results. The Investigator is encouraged to share the summary results with the trial patients, as appropriate.

15.4. Publication

The sponsor will comply with the requirements for publication of study results in a publicly available trials registry such as clinical trials.gov. Results may be published in peer-reviewed journals and presented at scientific meetings. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. In accordance with standard editorial and ethical practice, the sponsor supports publication of multicenter studies only in their entirety and not as individual site data. Sponsor will allow the Investigator to review the manuscript before publication by Sponsor. If the Investigator wishes to publish anything related to the trial, then they must provide the Sponsor with the draft publication and allow them no less than 30 days to review the document. The Investigator cannot publish without written authorisation from the Sponsor.

15.5. Data Management

For this trial, patient data will be collected using an eCRF and combined with data provided from other sources in a validated data system. Patient's identifiable data (e.g., name, initials, address etc.) will not be collected in the eCRF or transferred to Invex Therapeutics. Clinical data management will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the

statistical analysis or the credibility of the Clinical Study Report. Original CRFs will be retained by Invex Therapeutics; the Investigator will also retain a copy.

Management of clinical data will be performed in accordance with the applicable Sponsor standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Affairs and World Health Organisation Drug dictionary.

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)

b. Maintain SOPs for using these systems

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)

d. Maintain a security system that prevents unauthorised access to the data

e. Maintain a list of the individuals who are authorised to make data changes

f. Maintain adequate backup of the data

g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)

Training on the use of the electronic data collection system will be provided to all relevant trial site staff.

15.6. Independent Adjudication Committee

The IAC will consist of international medical experts in neurology or ophthalmology who are independent of the Sponsor team.

The role of the IAC will be:

- To support the Investigators with opinions on the eligibility of potential patients
- To provide opinions regarding treatment failure and need for rescue medications required during the trial

Further details on the composition, activities and responsibilities of the IAC can be found in the IAC charter.

15.7. Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) consisting of experts in neurology, neuro-ophthalmology and ophthalmology-will oversee the conduct of the study and ensure the safety of patients. The role and responsibilities of the DSMC, as well as the data review process are outlined in detail in a separate charter. DSMC reviews of safety data will be planned every 6 months (anticipating the first meeting will occur at approximately 6 months or when 25% of the patients recruited). In addition, unscheduled ad-hoc DSMC meetings will be triggered in case of emerging safety concerns. Based on clinical data reviewed, the DSMC may recommend an amendment to the study protocol or premature termination of the study. Such DSMC recommendations will be submitted to all IRB/IEC and health authorities.

Details on the composition, activities and responsibilities of the DSMC can be found in the DSMC charter.

15.8. Insurance, Indemnity and Finance

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this trial against future claims by trial patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all trial procedures have been carried out according to this protocol.

The financial aspects of the trial are addressed in a separate agreement.

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17. APPENDICES PROVIDED FOR TRIAL INVEX-CLIN-IIH-301

17.1. Appendix 1: LP SOP

Diagnostic lumber puncture

The diagnostic lumbar puncture (LP) is performed by the site as part of routine care to confirm the diagnosis of Idiopathic Intracranial Hypertension (IIH). This is not a research LP. For the patient to be eligible for the IIH Evolve trial the diagnostic LP must have the opening pressure measured in the lateral decubitus position in line with the guidance below. The LP must be within 4 weeks of commencing screening.

Research lumbar puncture

A research LP is performed at the end of the Randomised Period/ Week 24/ Visit 10. This is the primary outcome for the trial. In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10.

Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days. We recommend that the LP should be performed after visual assessment.

The LP should be performed by a trained clinician or health care professional according to local standard of care. The only mandatory requirement for the trial is that the measurement of LP opening pressure is conducted as per below.

Procedure

Suggested equipment required:

- Antiseptic cleaned trolley;
- Cleaning solution (Iodine or chlorhexidine)
- 2 pairs of sterile gloves;
- Sterile wound pack;
- Lumbar puncture manometer (up to 3 should be available) with corresponding 3 way valve stopcocks (should be included in pack);

- Needle point 20 gauge lumbar puncture needle;
- 10ml syringe x 1;
- Green syringe needle, blue syringe needle and orange syringe needle;
- Gauze pads x 1;
- 3 sterile universal pots;
- Sterile dressing.

Suggested technique

For a standard (non-image guided) LP:

- Ask the participant to lie in the lateral left position; they should be relaxed.
- The legs must be flexed at the hip at a 90˚ angle (support may be need to maintain this position).
- The L3/4 intervertebral space should be located using anatomical landmarks (the midline between the posterior superior iliac crests). If this is difficult, consider using ultrasound to identify the correct structures: IV space and spinous processes of L3 and L4. The space above or below may also be accessed if needed.
- Mark the location of needle entry.
- Clean a large circumference around the needle entry site using 70% alcohol or chlorhexidine using a sterile technique.
- Infiltrate 1-2% lidocaine subcutaneously and into the vertebral ligaments. Aspirate prior to infiltration to avoid intravascular injection. No more than 3mg/kg should be infiltrated (1% contains 10mg per 1ml).
- Once the area is appropriately anaesthetised, insert the needle bevel up, horizontally to the marked area and towards the umbilicus.
- Once a ‘give’ is felt, withdraw the stylet and ensure flow of CSF.

LP opening pressure measurement (mandatory)

- Pressure readings MUST be taken with the patient lying in the lateral left (or right) decubitus position.
- Connect the manometer and record the opening pressure:
    - If the patient’s thighs are compressing their abdomen then very slowly extend the legs at the hip joint to ensure the abdomen is not compressed.
    - Ensure the patient is not speaking or breath holding (avoid valsalva)

  - Allow time (sometimes around 5 minutes), for the pressure to become consistent (small fluctuations in the pressure with respiration should be seen) before a reading is taken
- Collect a sample of CSF in sterile universal container (size typically 25-30ml), and collect a 3ml CSF sample for the research trial. This should immediately be stood upright in a wet ice bath until processing. Process should be within 30 minutes of collection (see the Laboratory manual).
- There is no need to record a closing pressure for the trial.
- Replace the stylet, withdraw the needle and place a sterile dressing over the area.

<u>For an image guided-LP:</u>

This may be performed using guidance by ultrasound, x-ray or computerised tomography (CT). This should be performed by a suitability qualified health care professional (e.g. radiologist). The positioning for a patients undergoing an image guided LP vary internationally. For this trial the initial position for an image guided LP can be according to local expertise but the LP pressure measurement MUST be conducted in the lateral decubitus position as described above. This ensures standardisation across the trial.

Post procedure advice:

This should be in line with local hospital care pathways. We would suggest:

- Lie flat for approximately 30 minutes (there is no evidence to support that lying flat for any duration reduces a post LP headache). Pragmatic advice on mobilisation when the patient has recovered is advised.
- Simple analgesia may be prescribed and dispensed for post-procedure pain (headaches or back pain);
- Oral fluids may help with post-procedure headache (non-evidenced based recommendation).
- Remind the participant of the possible adverse effects.

17.2. Appendix 2: IIH Diagnostic criteria [Mollan, 2018]

A. Papilloedema

B. Normal neurological examination (except sixth cranial nerve palsy)

C. Neuroimaging: normal brain parenchyma (no hydrocephalus, mass, structural lesion or meningeal enhancement). Venous thrombosis excluded in all.

D. Normal CSF constituents (less than or equal to 7 white cells per mm^3 with normal protein and glucose

E. Elevated lumbar puncture pressure ≥ 25cm CSF

17.3. Appendix 3: 36-item short from survey

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

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Santa Monica, California 90401-3208

17.4. Appendix 4: EuroQol -5 dimension-5 level survey

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

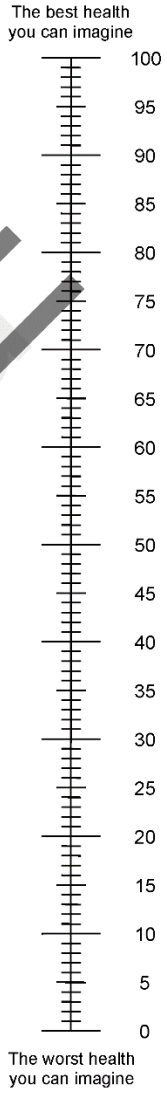
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



17.5. Appendix 5: Headache Impact Test-6

HIT-6™
(VERSION 1.1)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1	When you have headaches, how often is the pain severe?	Never	Rarely	Sometimes	Very Often	Always
2	How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?	Never	Rarely	Sometimes	Very Often	Always
3	When you have a headache, how often do you wish you could lie down?	Never	Rarely	Sometimes	Very Often	Always
4	In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
5	In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
6	In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?	Never	Rarely	Sometimes	Very Often	Always

COLUMN 1 (6 points each)	+	COLUMN 2 (8 points each)	+	COLUMN 3 (10 points each)	+	COLUMN 4 (11 points each)	+	COLUMN 5 (13 points each)

To score, add points for answers in each column.
Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36-78.

HEADACHE IMPACT TEST™

What Does Your Score Mean?

If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your doctor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

About HIT

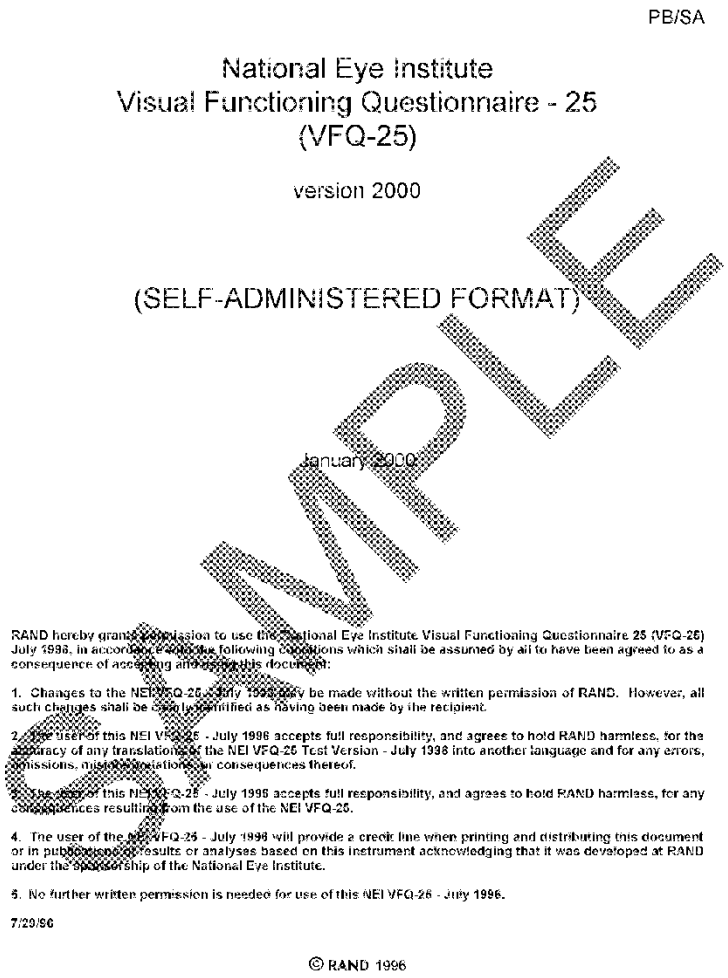
The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36®* health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

SF-36® is a registered trademark of Medical Outcomes Trust and John E. Ware, Jr.

HIT-6 Scoring Interpretation English Version 1.1

17.6. Appendix 6: Visual Function Questionnaire-25 & 10-item Supplement



PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

SAMPLE

RAND hereby grants permission to use the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

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7/29/96

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The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.
2. Please answer every question (unless you are asked to skip questions because they don't apply to you).
3. Answer the questions by circling the appropriate number.
4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.
5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.
6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your overall health is:**

(Circle One)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. **At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

(Circle One)

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

15. Are you currently driving, at least once in a while?

(Circle One)

Yes..... 1 *Skip To Q 15c*

No 2

15a. **IF NO: Have you never driven a car or have you given up driving?**

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. **IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?**

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. **IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have**

(Circle One)

No difficulty at all 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

SAMPLE

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0 1 2 3 4 5 6 7 8 9 10

Worst Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0 1 2 3 4 5 6 7 8 9 10

Worst Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?.....	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

10-ITEM NEURO-OPHTHALMIC SUPPLEMENT TO THE NEI-VFQ-25

The following are additional questions and statements about problems that involve your vision or feelings you may have about your vision condition. After each question, there will be a list of possible answers. Please choose the response that best describes your situation.

Please answer all questions as if you were wearing your glasses or contact lenses (if any). Please take as much time as you need to answer each question.

1. How much difficulty do you have performing tasks when your eyes are tired?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

2. Because of your vision, how much difficulty do you have identifying objects or performing tasks in bright sunlight?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

3. Because of your vision, how much difficulty do you have parking a car?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

4. Because of your vision, how much difficulty do you have using a computer?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

For each of the following statements, please indicate if it is definitely true, mostly true, mostly false, or definitely false for you or if you are not sure.

5. I have a feeling that my two eyes see differently, even with correction (glasses or contact lenses).
(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

6. I have a feeling that my eye or eyelid appearance is unusual.

(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

For each of the following, please indicate if it is true for you all, most, some, a little, or none of the time.

7. My vision is blurry, not clear, or "fuzzy."

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

8. I have trouble focusing on or following moving objects.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

9. I have double vision with both eyes open that is not present when either eye is covered.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

10. My eyelid(s) droop.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

17.7. Appendix 7: Patient Global Impression of Change

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is

✓*one box only:*

[1] ☐ Very much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very much Worse

17.8. Appendix 8: Contraception

Birth control methods which may be considered as highly effective (that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods).

Patients should be instructed not to take their oral contraceptive within 1 hour prior to administration of trial medication.

Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [1]
- sexual abstinence [2]

[1.] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant.

[2.] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Study Number: INVEX-CLIN-IIH-301 Protocol	Compound No.: Presendin Version: 4.0

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

Effective Date: 09-Jul-2022

Short Title: A Phase III trial to determine the efficacy and safety of Presendin in IIH – IIH EVOLVE

Abstract: Idiopathic intracranial hypertension (IIH) has significant associated morbidity and reduced quality of life. There is a significant risk of visual loss and patients also typically suffer with chronic disabling headaches.

This trial has been designed to evaluate the efficacy and safety of a new release formulation of exenatide (Presendin) in the reduction of intracranial pressure (ICP) in patients with IIH. The primary outcome will be determined by change in ICP, as measured by lumbar puncture (LP).

Eligible, consenting patients will be randomised in a ratio of 1:1 to receive Presendin or placebo as a weekly dose for 24 weeks.

Author	Department	Company
Emma de Launay	Clinical Operations	Invex Therapeutics Ltd.

Invex Therapeutics

[redacted]

SPONSOR SIGNATURE PAGE

Sponsor Signatory:

A Sinclair — 21.8.2022

Doctor Alexandra Sinclair
MBChB, PhD, FRCP

Chief Scientific Officer

Invex Therapeutics Ltd.

[redacted]

Date

SPONSOR INFORMATION PAGE

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Invex Therapeutics Ltd
[redacted]

INVESTIGATOR SIGNATURE PAGE

I, the undersigned, have read and understood the protocol and am aware of my responsibilities as an Investigator. I agree to conduct the study in accordance with this protocol, the Trial Reference Manual and any subsequent amendments, the Declaration of Helsinki, ICH GCP guidelines, and the laws and regulations of the country in which the study is being conducted.

Investigator Name and Qualifications: _____

_____ _____

Investigator Signature Date

[Investigator Affiliation]

INVESTIGATOR INFORMATION PAGE

Details will be provided in the Investigator Site File

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ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCRF	Electronic Case Report Form
BMI	Body Mass Index
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DGM	Data-Generating Models
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
GCL	Ganglion Cell Layer
GLP-1	Glucagon Like Peptide-1
HVF	Humphrey Visual Field
ICF	Informed Consent Form
ICP	Intracranial Pressure
IAC	Independent Adjudication Committee
ICH-GCP	International Council of Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
IIH	Idiopathic Intracranial Hypertension
ITT	Intention-to-Treat
LP	Lumbar Puncture
MAR	Missing At Random
MD	Mean Deviation
MHD	Monthly Headache Days
NRS	Numeric Rating Scale
OCT	Optical Coherence Tomography
PK	Pharmacokinetic
PP	Per Protocol
QTcF	QT Interval corrected according to Fridericia's formula
RNFL	Retinal Nerve Fibre Layer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	36-item short form survey
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event

ULN	Upper Limit of Normal
VFQ-25-10 item	Visual Function Questionnaire-25 and 10-item supplement

PROTOCOL SUMMARY

Rationale

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends.

IIH has significant associated morbidity and reduced quality of life. Elevated ICP causes papilloedema universally at disease onset and can lead to permanent visual loss. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Besides risk of visual loss, the most disabling aspect for patients is severe chronic headaches driven by elevated ICP. Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but the failure rates are high and frequent complications and side effects occur.

A modified release formulation of exenatide (Presendin) has been developed and this trial has been designed to evaluate the efficacy and safety of Presendin in IIH. The modified release formulation has been chosen to enable a once weekly dosing.

Objectives

Primary Objective

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

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation (PMD) as measured by the Humphrey Visual Field analyser (24-2 SITA (Swedish Interactive Testing Algorithm)-Standard)
- Papilloedema as measured by optical coherence tomography imaging (retinal nerve fibre layer (RNFL) thickness and optic nerve head volume measurements)

- Monthly headache days (MHD)
- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

Safety Objectives

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

Exploratory Objectives

To determine the effect of Presendin on:

- Macular ganglion cell layer/complex thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes (PROs)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Endpoints

Primary Endpoint

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

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

Secondary Endpoints

- Perimetric Mean Deviation
- Retinal nerve fibre layer thickness
- Optic nerve head size
- The number of monthly headache days (MHD). Monthly headache days will include 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 require acute headache analgesia.
- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs)
- Resting 12-lead ECG
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

Exploratory Endpoints

- Macular ganglion cell layer/complex thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes:
  - Visual Function Questionnaire-25 and 10-item supplement (VFQ-25-10 item supp)
  - Headache Impact Test -6 (HIT-6)
  - 36-item short from survey (SF-36)
  - EuroQol -5 dimension -5 level (EQ-5D-5L) survey
  - Patient Global Impression of Change (PGIC)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Trial Design

This is a randomised, placebo-controlled, double-blind, multi-centre trial requiring 240 adult randomised patients with IIH to determine the efficacy and safety of Presendin.

Consenting patients with a diagnosis of IIH will enter a 1-week screening period, in which there will be no investigational treatment, to gather baseline measurements and to check eligibility. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period due to the real risk of visual loss. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Wall, 2014, Markey, 2017 and Mollan, 2021]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

At the screening visit, patients will be provided with training on the self-administration of the trial medication and provided with a leaflet to take home. Patients will be asked to self-administer one (1) dose of placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed a screen failure and will not be randomised into the trial. Eligible patients will then be randomised to receive either Presendin or matching placebo for 24 weeks in

a 1:1 ratio. After completion of the randomisation period patients will have an end of treatment clinic visit. Five weeks after the end of treatment visit, an end of trial safety follow up telephone visit will also be performed.

The duration of the double-blind treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy over a 3-month time horizon. Additionally, an alternative off label drug used in IIH (acetazolamide) evaluated efficacy over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk. The duration of the trial for each patient will be up to 30 weeks, which includes a 1-week screening period, a 24-week randomised double-blind treatment period, and a treatment follow-up period of 5 weeks.

Trial Population

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of new IIH by consensus criteria (see Section 16.2, Appendix 2), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Newly diagnosed patients with screening commenced no more than 4 weeks after the diagnostic LP
4. Lumbar puncture opening pressure ≥ 25 cm cerebrospinal fluid (CSF) at diagnosis
5. Presence of bilateral papilloedema (Frisén grade ≥1). Verification of papilloedema by the OCT Reading Centre. Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerves should be conducted for evaluation by the Independent Adjudication Committee (IAC)
6. Perimetric Mean Deviation (PMD) defined as between -2 to -7 decibels (dB) in at least one eye. Eyes meeting this criteria will defined as ‘study eyes’
7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses, (reliability confirmed by the Visual Field Reading Centre) in study eyes
8. Two or more headache days over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period

9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.8, Appendix 8 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Able to provide written informed consent

Patients must not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusion criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth or seventh nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
6. 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

Vision related exclusion criteria:

7. Any disease other than refractive error that causes visual loss in the study eyes. Where there is uncertainly this would be determined by the Independent Adjudication Committee [IAC]
8. Refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in study eyes. In addition, participants with myopia of worse than -6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes. Where there is uncertainly this would be evaluated by the Independent Adjudication Committee [IAC]

Headache related exclusion criteria:

10. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

11. Untreated previously diagnosed obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
12. Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
13. COVID-19 vaccine within 2 weeks prior to screening
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which may affect the safety of the patient
16. History of drug-induced immune-mediated thrombocytopenia from exenatide products
17. Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
18. Using any glucose-lowering medication
19. Currently taking warfarin
20. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is

predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)

21. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
22. Any of the following abnormalities in clinical laboratory tests at screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
23. Using recreational or illicit drugs at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
24. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period
25. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
26. Any contraindication to lumbar puncture procedure in the opinion of the investigator
27. Has participated in any other interventional trial within 1 month prior to the screening visit.
28. Is pregnant or breastfeeding

Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2

Trial Assessments

Table 1: Time and Events

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Informed consent	X											
Inclusion/Exclusion criteria	X	X (review)										
Demography (sex, age, ethnicity)	X											
Medical & Ophthalmic History	X											
Concomitant medication history	X											
Headache history	X											
Concomitant medication review		X	X	X	X	X	X	X	X	X		X
Headache preventative medication review	X	X	X	X	X	X	X	X	X	X		X
Train and dispense headache diary	X											
Review headache diary[1]		X	X	X	X	X	X	X	X	X		
Vital signs[2]	X	X		X	X	X	X	X	X	X		(X)
Height	X											

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Body weight and BMI	X	X			X	X	X	X	X	X		
Adverse Events[15]		X	X	X	X	X	X	X	X	X		X
Physical Examination (T = targeted)	X (Full)	X (T)				X (T)		X (T)	X(T)	X (T)		(X)
Pregnancy Test[3]	X (Serum)	X		X	X	X	X	X	X	X		X
Electrocardiogram	X	X		X	X	X	X	X	X	X		(X)
OCT Imaging	X	X		X	X	X	X	X	X	X	X	
Assessment of Papilloedema Frisén grade[4]	X	X										
Perimetry	X	X		X	X	X	X	X	X	X	X	
Visual Acuity Testing (LogMAR score)	X	X		X	X	X	X	X	X	X	x	
Patient Reported Outcomes (HIT-6, SF-36, EQ-5D-5L, VFQ-25 & 10-item supp)		X			X	X	X	X	X	X		
Health Utilisation Form		X	X	X	X	X	X	X	X	X		
PGIC assessment										X		
Laboratory assessments[5]	X	X		X	X	X	X	X	X	X		(X)

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Pharmacokinetic (PK) sampling[6]		X[7]		X	X	X	X	X	X	X		
Anti-Drug Antibodies (ADA) sampling		X		X	X	X	X	X	X	X		
Lumbar Puncture[8]										X[9]		
Trial medication training[10]	X	X										
Randomisation		X										
Trial medication Dispensing	X	X			X	X	X	X	X			
Trial medication Accountability				X	X	X	X	X	X	X		

1 The screening period must be a minimum of 7 days, up to a maximum of 10 days. Patients who do not meet the eligibility criteria based on diary review at randomisation/baseline (e.g., too few headache days or unacceptable concomitant medication use) will be considered screen failures; however, if the patient wishes and the Investigator is in agreement, he/she can be re-screened as a new patient. If the screening period exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit. Trial site research team should review diaries remotely on a weekly basis to ensure compliance and follow up any patients with missing data

2 Vital signs to include: blood pressure and heart rate

3 Women of child-bearing potential. Serum pregnancy test to be conducted at screening, thereafter, highly sensitive urine pregnancy tests will be conducted. Visit 11 urine pregnancy test may be conducted at home

4 Frisén grade will be evaluated locally and the presence of papilloedema verified by the OCT Reading Centre at screening to confirm eligibility. Indeterminate cases should be referred to the IAC (and supplemented with fundus photography and ultrasound scan of the optic nerve) to confirm papilloedema prior to randomisation visit

5 Haematology, coagulation, biochemistry and urinalysis

6 All actual sampling times and dosing times will be recorded

7 Baseline Post-dose PK blood sample

[8] The diagnostic LP will be the baseline LP and must be performed in lateral decubitus position. Patients with ICP <25 cm CSF at diagnosis will be excluded

[9] Lumbar puncture to be performed after visual assessment. LP to be performed as per Appendix 1. CSF sample from visit 10 LP will be retained for future potential analysis

[10] Patients will be provided with training on the self-administration of the trial medication. The patient will be asked to self-administer placebo at visit 1 to demonstrate ability to self-inject. Patients who are not comfortable to self-inject will be excluded

[11] If patients discontinue in the randomised double-blind treatment period they will be encouraged to return for all trial visits up to visit 11. If a patient does not want to return for all visits then they will be asked to return at a minimum for visit 11 procedures for safety follow up

[12] In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days

[13] Optional unscheduled visit for visual testing (HVF, OCT, LogMAR) for patients in whom there is concern about visual decline or who perform inadequately or where there is technical failure (more than 15% false positive responses or inadequate performance indicated by the Visual Field Reading Centre for HVF; or OCT imaging not of satisfactory quality as determined by the OCT Reading Centre)

[14] In the event of any abnormal safety assessments identified at end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments

[15] Reporting of AEs/SAEs will continue up to the final follow up visit 11

1. INTRODUCTION

1.1. Background and Rational

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends [Mollan, 2019a]. There is a high rate of repeat hospital admission in IIH (increased by 446% in last decade), reflected in escalating healthcare costs (in England £462 million/year predicted by 2030 [Mollan, 2019a] and more than $444 million in the USA [Friesner, 2011]).

The cause of IIH is not fully understood. Recent research suggests that IIH is a disease of systemic metabolic dysregulation characterised by central adiposity [Hornby, 2017], double the risk of cardiovascular disease in excess to that mediated by obesity [Adderley, 2019] and dysfunctional adipocyte metabolism primed for weight gain [Westgate, 2021]. Patients are also insulin resistant and have a unique hormone signature of androgen excess both systemically and in the cerebrospinal fluid.[O'Reilly, 2019]

Morbidity in IIH is due to the elevated intracranial pressure which can cause severe papilloedema (swelling of the optic nerve) which can ultimately lead to blindness. The risk of permanent visual loss is a major concern in IIH. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Headache is an additional major disabler and affects the majority of IIH patients (over 90%) [Yri, 2014; Markey, 2016; Mulla 2015] in the long term. Headaches significantly reducing quality of life [Mulla, 2015; Digre, 2015] are driven by raised intracranial pressure and often have a migraine- like phenotype (> 90%) [Mollan 2021a].

Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. [Piper, 2015; Mollan, 2018; Hoffmann, 2018]. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but there is a high failure rate and frequent complications. The lack of licenced or targeted treatments in IIH perpetuates poor outcomes for patients. A priority setting exercise was run by patients with IIH (James Lind methodology) [Mollan, 2019c] establishing effective therapy was the top priority from the patient group.

This trial will investigate an alternative therapeutic option for lowering ICP and thereby reducing papilloedema and consequently reducing the risk of visual loss. By reducing ICP it would also aim to improve headache, improving overall patient quality of life in IIH [Mollan 2021a].

Gut neuropeptides are increasingly being recognised for their role in the central nervous system (CNS). A principal gut neuropeptide is glucagon like peptide-1 (GLP-1), which is known to stimulate insulin release, proliferation of pancreatic beta cells and control of glucose regulation in diabetes [Campbell, 2013]. Exenatide is a GLP-1 receptor agonist. It has also been shown to have some actions in the CNS; GLP-1 is involved in regulating satiety and weight through signalling at the hypothalamus [Astrup, 2009]. There is also evidence that GLP-1 may have a role in fluid secretion. In the renal proximal tubule GLP-1 acts to reduce sodium resorption to promote diuresis [Gutzwiller, 2004; Websky, 2014]. The choroid plexus is the fluid secreting structure within the brain producing the majority of CSF. The structure of the choroid plexus epithelial cells is analogous to an inverted renal proximal tubule with a similar mechanism of secretion and hence GLP-1 receptor agonists may also reduce CSF secretion in the brain, leading to a decrease in ICP in patients with IIH.

Exenatide as well as other GLP-1 receptor agonists can lead to weight loss. In diabetic patients, weight loss of 2.8 - 4.4 kg has been reported over 6 months [Di Dalmazi 2020; Pujante 2012]. Whilst in non-diabetic overweight and obese patients exenatide caused sufficient weight loss between 2.0 – 5.1 kg [Moreno 2012]. In overweight and obese patients with polycystic ovarian syndrome exenatide led to 2kg more weight loss compared to placebo in over 12 weeks [Liu 2017]. Weight loss with exenatide therapy is increased in the setting of calorie restriction [Rosenstock 2010]. Weight loss is a desirable effect of exenatide as weight loss is therapeutic in IIH. Changes in body weight will be monitored during the trial and the impact on outcomes measures evaluated.

Exenatide is the active ingredient in Byetta, an immediate-release (IR) formulation and Bydureon, an extended-release (ER) formulation. These have been licenced for use in adults with type-2 diabetes since 2005 and 2014, respectively. Therefore, there is a wealth of available safety data from both clinical trials and real-world experience. Exenatide has been identified as a potential candidate for the treatment of neurological conditions involving raised ICP and a polylactic-co-glycolic acid (PLGA) ER exenatide formulation under the name Presendin, has been developed by Invex Therapeutics for the treatment of IIH.

Byetta has a known issue of rapid elimination of the product when given to humans, and because of this it needs to be administered twice daily to achieve its pharmacological effects. The data on file from the IIH Pressure trial has shown that in patients with IIH, exenatide administered twice daily was well tolerated and produced a positive effect on reducing CSF pressure. However, it is considered that the immediate release formulation of exenatide is not ideal for treating patients with IIH on a long-term basis. Presendin has been developed as an extended release formulation to allow for a reduction in dosing frequency to once weekly and more consistent therapeutic plasma levels.

This trial is designed to investigate the efficacy and safety of a modified release formulation of exenatide (Presendin) in patients with IIH.

Intracranial pressure

IIH is a debilitating condition characterised by raised ICP, which is clinically measured by LP [Mollan, 2018]. The units for measurement of LP are cm CSF and cm H_2O and these should be thought of as interchangeable and reflect the measurement of the height of the CSF column at LP. The measurement must be taken in the lateral decubitus position. Lumbar puncture is conducted to make a diagnosis of IIH. Lumbar puncture may be conducted in a clinical setting during the disease course to both monitor and treat the condition. Frequent therapeutic LPs are no longer recommended by the International IIH guidelines [Mollan, 2018]. This is because LP can be traumatic for patients and can occasionally cause significant complications (meningitis, spinal haematoma, pain) [Wright, 2012]. Hence, unnecessary LP's should be avoided. In some patients LP can alter other outcome measures, including measurements of papilloedema and headache [Yiangou, 2019]. Hence ideally, LP should be performed after these measures and symptoms have been assessed. Lumbar puncture can cause post-dural puncture headaches. The risk is 9-36% using a traumatic needle and 3-19% using an atraumatic needle [Wright, 2012]. Post-dural puncture headaches typically last less than a week but in some patients this can be longer [Yiangou, 2019]. Lumbar puncture pressure assessment of ICP reflects disease activity and is a useful and recognised outcome measure that has been utilised in other IIH trials [Markey 2020; Mollan 2021b].

Due to the invasive nature of LP, non-invasive measures of ICP are valuable. The majority of techniques historically evaluated as non-invasive surrogate measures of ICP lack sufficient quantification to be used clinically or in clinical trials. Optical coherence tomography (OCT) measures of the optic nerve have been shown to provide a useful surrogate measure to quantify changes in ICP [Vijay, 2020]. For example, at 12 months, Vijay *et al* showed that a change in optic nerve head height of 50 µ predicted a 5 cm CSF change in ICP [Vijay, 2020].

Visual Function

Perimetry is used to measure visual function in IIH clinical practice. This is assessed using a Humphrey Field Analyzer (program 24-2 SITA standard using a size III white stimulus) test. Patients are often unaware of their visual field loss until this becomes more severe and compromises daily activities. In patients with severe papilloedema optic atrophy can develop (measured objectively as loss of the macular ganglion cell layer on OCT imaging) and the loss of visual field becomes permanent. Patients at risk of rapidly progressive visual loss (also termed fulminant IIH) should receive emergency surgical intervention (most commonly a CSF shunt operation) [Mollan, 2018]. Patients requiring

emergency surgery will not be recruited into this trial. Medical therapy is used to treat those IIH patients not requiring emergency surgical intervention and will be included in this trial. But it is expected that approximately 5-10% will go on to need more aggressive intervention.

Measuring visual function with perimetry has a number of challenges in IIH which need to be carefully considered. The visual field test is dependent on technician and patient performance and can be prone to variability and inaccuracy [Cello, 2016; Wall, 2016]. Patients can perform poorly on automated perimetry [Cello, 2016], and there is a learning effect [Kutzko, 2000; Wall, 2016]. There are further confounding factors when considering interpretation of automated visual field testing in IIH. The high prevalence of functional vision loss, presenting as non-organic visual fields results in this disease, may bias trial outcomes [Kutzko, 2000; Ney, 2009]. Additionally, impaired executive function and attention deficits have been noted in IIH [Sørensen, 1986], and have been shown to impair performance of visual field testing in IIH [Grech, 2021].

The protocol has been designed with these challenges in mind and visual field testing performance will be assessed at trial entry and throughout with opportunity for repeated assessment if there is performance failure (a performance failure is defined as a substantial worsening of the perimetric mean deviation due to human factors rather than visual damage) [Cello, 2016].. The visual fields will be assessed by the Visual Field Reading Centre.

Papilloedema by change in optic nerve head size measured by OCT imaging.

Papilloedema is a reliable sign of raised ICP [Dunn, 2002]. Change in papilloedema has been used by all the randomised control trials in IIH to date to determine clinical improvement [Ball, 2011; Wall, 2014; Mollan 2021b]. Change in papilloedema has been graded by experts using the Frisén classification, although it is more reliably measured by OCT imaging [Ball, 2011; Wall, 2014]. Professional bodies and the literature endorse the use of OCT imaging for monitoring papilloedema in IIH [Mollan, 2018].

OCT imaging measures various aspects of the optic nerve. The retinal nerve fibre layer (RNFL) and optic nerve head volume are measurements that both reflect swelling of the optic nerve and hence the extent of papilloedema. Measures of macular volume can quantify the ganglion cell layer (GCL) thickness which reflects axonal loss. Optic nerve head measures on OCT correlate with visual field sensitivity loss [Salgarello, 2001]. Analysis has shown that OCT measures of the RNFL significantly reflect changes in visual field perimetric mean deviation (MD) (for every 10µm increase in RNFL there was associated with a 0.6dB decrease in MD) [Rebolleda, 2009]. Optical coherence tomography measures of the macula volume have been shown to predict axonal loss of the optic nerve [Albrecht, 2017]. Most importantly, ganglion cell volume has been shown

to significantly correlate with the Humphrey visual field MD [Vijay, 2020]. This indicates that the GCL can be measured to reflect visual function. In other neurological diseases OCT has also been found to measure neuronal loss and correlated with visual loss [Petzold, 2010]. In summary, OCT assessment of the optic nerve and GCL represent objective measures of papilloedema and optic nerve axons which reflects visual function.

The scan quality can be compromised if the automated software segmentation of the OCT is not accurate. This occurs particularly in those optic nerves with more pronounced papilloedema [Aojula, 2018]. Hence the quality and segmentation of all OCT scans will be assured by the OCT Reading Centre and scans will be repeated if of insufficient quality.

Headache

Headache is the predominant presenting feature in IIH [Mollan, 2019a]. Patient morbidity is high because of disabling headaches and they have been found to be the key driver for poor quality of life [Mulla, 2015; Digre, 2015]. Research into headache treatments were endorsed as clinically relevant by a priority setting partnership which included the opinions of the patients' carers and physicians [Mollan, 2019c].

It has been well documented that headache characteristics in IIH are typically migraine-like (up to 90%) [Mollan, 2019b; Mollan 2021a]. The headache location can be halo-cranial, frontal, temporal or parietal with features including nausea, throbbing pain, photophobia and phonophobia [Yri, 2015]. A Danish trial of 44 IIH patients noted that 82% of patients had migraine-like attacks [Yri, 2014]. A prospective trial in 52 IIH patients in the UK characterised 80% of headaches as migraine-like [Yiangou, 2019]. As reported by the Idiopathic Intracranial Hypertension Treatment Trial, US, the headache phenotype was recorded as migraine or probable migraine in 68% of 144 patients with active IIH [Friedman, 2017]. A retrospective trial in Iran in 68 IIH patients characterised migraine-like headaches in 63% [Sina, 2017]. Other headache characteristics are typically tension-type or unclassified [Mollan, 2019b].

Hence whilst IIH headaches are not diagnostically the same as migraine according to the International Classification of Headache Disorders, 3rd edition Beta, they are very similar in character [Olesen, 2018]. The International Headache Society core outcomes for migraine are therefore applicable to IIH headaches [Tassorelli, 2018].

Headache in active IIH is driven by ICP. This is evidenced by the fact that removal of CSF fluid results in improved headache severity. In a prospective cohort study, headache severity improved in 71% following a standardised LP [Yiangou, 2019]. Ninety-five percent of IIH patients had improvement in headache symptoms at 1 month following

shunt placement [Daou, 2020]. Weight loss leading to reduction in ICP also significantly reduced headache [Sinclair, 2010].

Medications that reduce ICP have been shown to modulate headache. In an open label trial using topiramate and acetazolamide, both of which are known to modulate ICP [Scotton, 2019], relief of headache was reported after a mean treatment period of 3.75 months in the topiramate group and 3.3 months in the acetazolamide group [Çelebisoy, 2007].

Importantly, headache measures (severity and monthly headache days) in IIH significantly correlate with changes in ICP [Mollan 2021a]. The IIH weight trial [Mollan, 2021b], a randomised controlled parallel group multicentre trial in the United Kingdom, investigates weight management methods in IIH. Participants with active IIH (evidenced by papilloedema) and a body mass index (BMI) $\geq 35 kg/m^2$ were recruited. The primary outcome was ICP as measured by LP opening pressure at 12 months, with secondary outcomes of ICP at 24 months and headache outcomes at 12 and 24 months. Headache severity was correlated with ICP at baseline; change in headache severity and monthly headache days correlated with change in ICP at 12 months. Importantly those with the greatest reduction in ICP over 12 months had the greatest reduction in headache frequency and severity. This implies that treatment of ICP should improve headache in IIH.

The following headache outcomes are clinically relevant and are recommended by the American Headache Society [American Headache Society] and International Headache Society to identify patients who are benefiting from treatments. Headache outcomes are derived from a 28-day diagnostic headache diary. This is used in clinical trials to prospectively collect daily information on headache occurrence, severity, associated symptoms, and use of acute analgesic medications.

Although a headache diary is typically over 28 days, for IIH headache it was felt unethical to have patients off treatment for this more prolonged period during screening due to the real risk of visual loss. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Mollan 2021b]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

Monthly headache days

Monthly headache days (MHD) will include 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 require acute headache analgesia. This is the most relevant and objective measure of headache.

Moderate to severe monthly headache days

A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications. This outcome captures the more disabling headaches.

Moderate to severe MHD was recently reported as the primary endpoint in a prospective open label study providing evaluation of the effectiveness of erenumab, a calcitonin gene-related peptide (CGRP) monoclonal antibody, to treat headaches in IIH patients [Yiangou, 2021]. It is also used to measure headache in other secondary headache conditions such as persistent post traumatic headache [Aojula 2018; Ashina, 2020].

Headache responder rate (≥50% reduction in MHD)

Headache responder rate (≥50% reduction in MHD) is the proportion of patients achieving at least 50% reduction in the mean number of MHD, of any intensity, from baseline to the defined trial end point. This criterion is clinically relevant as it is used as an empirical review for continuing or discontinuing headache therapy [Diener, 2020]. Responder rates can be used in meta-analyses of placebo controlled randomised controlled trials.

Headache responder rate (≥50% reduction in moderate to severe MHD)

Headache responder rate (≥50% reduction in moderate to severe MHD) is the proportion of patients achieving at least 50% reduction in the moderate to severe MHD from baseline to the defined trial end point. It is well recognized that 50% responder rates may not fully capture the benefits of treatment [Matharu, 2017]. For example, a patient may improve from a disabling 20 severe headache days per month to 11 moderate headache days per month. Despite this considerable clinical benefit, such a patient would not be considered a responder because headache days were not reduced by ≥50%, and as a result might lose access to beneficial treatment. Hence, responder rates of ≥30% are also important [Vernieri, 2019]. In IIH, a disorder of chronic severe headaches, a clinically meaningful treatment responder rate has not been definitively established, although the International Headache Society Clinical Trials Subcommittee has suggested the use of a ≥30% reduction from baseline for chronic migraine.

Headache severity

Headache severity is an important measure and impacts quality of life. It is vital to consider some treatments which benefit headache may not reduce the MHD but if the severity is markedly improved this will lead to great overall functional benefit to the

patient and is clinically relevant [Silberstein, 2008]. Recording the decrease in intensity is an indicator of reduced disability, which is clinically meaningful.

Monthly use of acute headache rescue medications

Use of acute headache analgesics reflects a judgement of the inefficacy of the test treatment; hence it is a helpful secondary outcome. In Sinclair *et al.* reduction in analgesic days was significant and associated with clinical remission of IIH [Sinclair, 2010]. Additionally, a high portion of IIH, up to 48% [Yiangou, 2021] have medication overuse and medication overuse headache, and reduction in analgesic days mitigates these. Reduction in monthly use of acute headache analgesic is an additional endpoint that contributes to clinically meaningful results.

Quality of life in IIH

IIH has a detrimental effect on all aspects of the patient's quality of life; the majority of which is driven by headache [Kleinschmidt, 2000, Mulla, 2015; Daniels, 2007; Digre 2015]. IIH also impacts visual function with PMD correlating with quality of life [Bruce 2016]. Patient reported outcomes in clinical trials are essential not only to permit health technology assessments and cost effectiveness analysis, but also as key outcomes for a therapy's effectiveness [Deiner, 2019]. There is currently no IIH disease specific quality of life outcome measure.

Whilst there are differences in the choice of the tools used in the trials, they all commonly used the short-form 36 health survey (SF-36) [Mollan, 2021, Wall, 2014, Digre, 2015; Bruce, 2016; Ball, 2011]. The physical component score of the SF-36 has been shown to correlate significantly with changes in ICP [Grech 2021]. The EuroQol –5 dimension (EQ-5D-5L) [Euroqol, 1990] is typically employed for health technology assessments and cost effectiveness [Ottridge, 2017; Ball, 2011]. Using the EQ-5D-5L in isolation may lack sensitivity as compared to the SF-36 for IIH. The National Eye Institute Visual Function Questionnaire-25 and 10-item supplement [Mangione, 2001] has also been utilised to assess visual related quality of life in IIH and is associated with improvement in visual field [Bruce 2016; Mangione 1998; Raphael 2006]. The 10-Item neuro-ophthalmic supplement was found to be significantly discriminating in a previous IIH drug trial [Wall 2014].

1.1.1. Name and Description of the Investigational Product

Patients will receive active treatment, Presendin, or matching placebo.

Presendin is a modified release formulation of exenatide. Exenatide is a GLP-1 receptor agonist currently used in the management of type 2 diabetes. Presendin consists of a drug

part (white or greyish white powder in a clear vial) and a diluent part (colourless liquid in a pre-filled syringe). The drug part is suspended in the diluent part solution and administered as a suspension. The patient or responsible person will be responsible for rehydrating the product for injection. Presendin is administered as a once weekly SC sustained-release injection containing 2.0 mg exenatide. Matching placebo will also be supplied as 2 parts, as visually identical vial and pre-filled syringe. The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. Placebo is administered once weekly as a SC injection.

1.1.2. Non-clinical Studies

Exenatide, the active ingredient of Presendin, has been previously developed and licensed as Byetta for the treatment of type 2 diabetes. A wealth of historical toxicological and pharmacological safety data is available in the public domain. Please see the Investigator's brochure for data from rat and mouse studies which have investigated the Presendin formulation of exenatide.

In vitro and *in vivo* data suggests that the choroid plexus, the CSF secreting structure in the brain, contains GLP-1 receptors [Ast 2020]. Preclinical studies in rodents demonstrate that GLP-1 agonists can regulate cerebrospinal fluid dynamics and reduce ICP [Botfield, 2017].

Nonclinical pharmacology studies have shown that exenatide and GLP-1 agonists bind to and stimulate GLP-1 receptors equipotently. Due to the ability of exenatide to affect fluid homeostasis in the kidney, it was investigated for its potential to modulate CSF secretion and reduce ICP in rats. A single SC injection of exenatide rapidly (within 30 minutes) reduced ICP and maintained lower ICP for 6 days of dosing, suggesting that GLP-1 receptor agonists could provide an alternative treatment for conditions with raised ICP [Botfield, 2017].

Exenatide was subjected to full toxicological assessments during its nonclinical development programme, details of which are publicly available in the Byetta® Product Monograph, 2019 and the FDA Pharmacology Review, June 2004 (Section 15). In summary, no lethality or serious toxicity was observed in mice, rats and monkeys following single doses up to 1500 µg/kg, 3000 µg/kg and 5000 µg/kg respectively. In repeat-dose toxicity studies decreased body weight gain and food consumption, a known pharmacological effect of exenatide, were observed in all studies. Exenatide caused no mortality or target organ toxicities in mice, rats and monkeys at doses up to 760µg/kg/day (182 days), 250 µg/kg/day (91 days), or 150 µg/kg/day (273 days) respectively. Reproductive toxicity data from animal studies showed that Byetta had a toxicological effect on foetal development at three times the human exposure levels in treatment of

diabetes. A summary of the findings of the exenatide toxicological assessment programme is presented in the Investigator Brochure for Presendin.

1.1.3. Clinical Studies

Exenatide has undergone extensive healthy volunteer studies and clinical trials for over 15 years. It is licensed as a formulation for SC injection to be used in conjunction with diet and exercise to improve glycaemic control in adults with type 2 diabetes. Details of the trials conducted on exenatide, SC injection formulation, are presented in the Byetta Product Monograph (Section 15). Data from these studies are notable as the dose of exenatide to be used in the indication of IIH is intended to produce exposure levels not exceeding those experienced by patients receiving Byetta. It is anticipated that the proposed therapeutic dose of exenatide, in the modified release formulation Presendin, for treatment of IIH will be within the approved dose range of Byetta, achieving a level of total systemic exposure comparable with the immediate release Byetta formulation. Therefore, safety data available from the Byetta clinical development program are considered relevant and supportive of exenatide development in IIH.

The efficacy of exenatide (Byetta) was evaluated in a Phase 2 randomised, placebo controlled, double-blind trial of exenatide in patients with active IIH (IIH:Pressure Trial). Sixteen patients with a diagnosis of active IIH (LP opening pressure >25 cm CSF and papilloedema) were identified and recruited to the trial. Participants had a telemetric ICP monitor implanted and were randomised to either exenatide (first dose was 2. 0 mcg followed by 10 mcg BD sub-cutaneous) or a matched placebo; allocation was 1:1. The treatment duration was 12 weeks. The trial was powered to seek significance to at least alpha < 0.1 and power at least 80% using equal group sizes. Data was analysed by hierarchical regression analysis. 16 participants were recruited, 15 were randomised and completed the study. At baseline the mean age was 28 ± 9 years, BMI 38.1 ± 6.2 kg/m2, ICP 23.5 ± 3.9 (equivalent to 32.0 ± 5.3 cm CSF). The primary outcome, change in intracranial pressure between arms, was significant: at 2.5 hours -4.2 ± 2.1 mmHg (equivalent to 5.7 ± 2.9 cm CSF), p=0.04, at 24 hours -4.7 ± 2.1 mmHg (equivalent to 6.4 ± 2.9 cm CSF), p=0.03, and at 12 weeks -4.1 ± 2.2 mmHg (equivalent to 5.6 ± 3.0 cm CSF), p=0.05. A significant reduction in monthly headache days was also observed amongst those on exenatide (-7.7 ± 9.2, p-0.069). LogMar visual acuity also significantly improved in the exenatide treated arm (-0.1 ± 0.05, p=0.036). No significant weight loss was observed in either arm and hence weight change is unlikely to have contributed to the reduction kin ICP observed. Exenatide was safe and well tolerated: no treatment related SAE's were reported, 8 adverse events were reported in those taking exenatide. The most frequent adverse event, amongst those taking exenatide, was nausea (7 reports), the majority of these were mild and all reports were self-limiting. There were no patient withdrawals due to adverse events.

1.1.4. Trial Conduct

This trial will be conducted in accordance with the requirements of this document (the Clinical Trial Protocol), the Trial Reference Manual and also in accordance with the following as per country specific requirements:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)
- The United Kingdom Statutory Instrument 2004 No. 1031 and UKSI 2006 No.1928
- European Union Directives 2001/20/EC and 2005/28/EC
- United States Code of Federal Regulations Title 21
- The Australian Therapeutic Goods Act, 1989, amended December 2020 and Therapeutic Goods Regulations, 1990, amended January 2021
- Other country specific laws and regulations
- Any amendments to these regulations

1.2. Risk/Benefit Assessment

Current treatments for IIH have limited efficacy and can cause disabling side effects. Acetazolamide, the most commonly used drug (off licence) has a high side effect profile (48% discontinued in a clinical trial due to intolerable side effects) [Ball, 2011]. Although IIH is a rare condition, incidence is rising with rising obesity trends. Improving IIH morbidity with new therapeutics is clearly an unmet need.

Safety data for Presendin (exenatide) is based on the IB (Peptron Inc.). Warnings include pancreatitis, hypoglycaemia when used in combination with a sulfonylurea, renal impairment, severe gastrointestinal disease and hypersensitivity.

Invex Therapeutics has considered these warnings and has defined eligibility criteria to ensure patient safety is paramount. As such patients with known contraindications to GLP-1 agonists, such as pancreatitis, ketoacidosis, severe gastrointestinal disease and renal impairment, will not be included. Additionally, diabetic patients receiving glucose lowering medication will be excluded.

An Independent Adjudication Committee (IAC), as described in Section 14.5, will assist the Investigators (when required) with the eligibility criteria of the patients to be enrolled,

and also to determine treatment failures to ensure patient safety and the efficacy of the trial.

The most common adverse reactions experienced with exenatide are nausea, hypoglycaemia (only when used with other glucose lowering drugs, but these patients are excluded from the trial), vomiting, diarrhoea, feeling jittery, dizziness, headache and dyspepsia.

Patients receiving the active treatment during the randomised period may benefit by experiencing an improvement in their IIH symptoms, although this cannot be guaranteed.

2. OBJECTIVES

2.1. Primary Objective

To determine the efficacy of Presendin administered subcutaneously once weekly for 24 weeks to patients with IIH, as determined by change in ICP, as measured by LP at baseline and at 24 weeks.

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

2.2. Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation as measured by Humphrey Visual Field analysis (24-2 SITA-Standard)
- Papilloedema by change in optical coherence tomography (retinal nerve fibre layer (RNFL) thickness and optic nerve head size)
- Monthly headache days (MHD)
- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

2.3. Safety Objective

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

2.4. Exploratory Objectives

To determine the effect of Presendin on:

- Macular ganglion cell layer/complex thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes
- Body Mass Index
- Body Weight
- Health Utilisation

3. ENDPOINTS

3.1. Primary Endpoint

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

The baseline LP is the diagnostic LP. Week 24 LP to be performed as per Appendix 1.

3.2. Secondary Endpoints

- Perimetric Mean Deviation
- Retinal nerve fibre layer (RNFL) thickness
- Optic nerve head size
- The number of monthly headache days (MHD). Monthly headache days will include all headache days, defined as those with an onset, continuation or recurrence, any severity or phenotype of headache, lasting at least 30 minutes or which require acute headache analgesia.

- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

3.3. Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), , serious adverse events (SAEs)
- Resting 12-lead electrocardiogram
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

3.4. Exploratory Endpoints

- Macular ganglion cell layer/complex thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes (PRO):
  - Visual Function Questionnaire-25 and 10-item supplement
  - Headache Impact Test-6
  - 36-item short form survey

- EuroQol -5 dimension -5 level survey
- Patient Global Impression of Change

- Body Mass Index
- Body Weight
- Health Utilisation

4. TRIAL DESIGN

4.1. Summary of Trial Design

4.1.1. Trial Design

This will be a randomised, placebo-controlled, double-blind, multi-centre clinical trial in approximately 240 randomised patients with IIH.

The trial will begin with a 1-week screening period. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period. Headache diaries designed to measure headache frequency have been successfully utilised over shorter time periods in previous IIH trials and noted to be representative [NORDIC, 2018; Mollan, 2021b]. Hence the baseline headache frequency will be calculated over 1 week. Patients will be provided with training on the self-administration of the trial medication from the site trial coordinator and provided with a leaflet to take home at the screening visit. Patients will be asked to self-administer placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed screen failures, and not be randomised into the trial. The purpose of the screening period will be to establish baseline measurements and assess trial eligibility.

The screening period will be followed by a 24-week randomised double-blind treatment period in which patients will be randomised (1:1) to receive a SC dose of either Presendin (containing 2mg of exenatide (active group) or matching placebo (placebo group), self-administered once weekly.

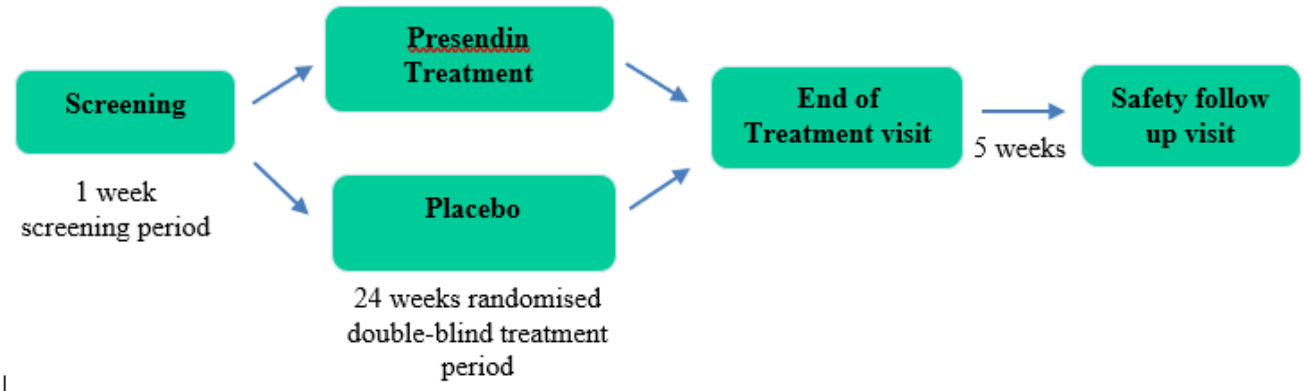
At the end of the randomised treatment period (week 24), all patients will have an end of treatment clinic visit. Five weeks after the end of that treatment visit, an end of trial safety follow-up telephone visit will be performed. In the event of any abnormal safety assessments or ongoing adverse event(s) identified at end of treatment; for example, an abnormal ECG or abnormal routine laboratory results, this visit may be performed at the clinic and a safety follow-up performed as appropriate.

The duration of the randomised treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy by 3 months. Additionally, an alternative off label drug used in IIH (acetazolamide) was evaluated over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk.

Assessments will be performed as outlined in Table 1.

A schematic diagram of the trial can be seen in Figure 1.

Figure 1: Schematic Diagram



4.1.2. Randomisation and Blinding

At the end of the Screening period, eligible patients will be randomised to receive either Presendin or matching placebo in a 1:1 ratio using a computer system to generate randomisation codes.

Investigators and other site personnel, patients, contract research organisation and Sponsor personnel will be blinded regarding the treatment during the randomised period. Only designated unblinded staff, not involved in the operational conduct of the trial, will be aware of the randomisation codes.

The placebo will have the same appearance and reveal no differences, during administration, to either the Investigator or the patient.

4.1.3. Duration of Patient Participation

The duration of the trial for each patient will be up to 30 weeks, which includes a 1-week screening period, a 24-week randomised treatment period and a treatment follow-up period of 5 weeks.

4.2. Stopping Rules

4.2.1. Trial Stopping Rules

There are no trial-specific stopping rules. The Sponsor maintains the right to stop the trial at any point. If this is done, then the Sponsor will provide the Investigators with the rationale for such early termination.

4.2.2. Individual Stopping Rules

Patients will be withdrawn from the trial medication if they are unable to tolerate the trial medication and will continue to attend trial visits as per protocol. See Section 11 for further details. A Data Safety Monitoring Committee (DSMC) will be involved in decisions for patient safety (Section 14.6).

4.3. End of Trial

The end of trial is defined as last patient last visit.

5. TRIAL POPULATION

5.1. Number of Patients

It is anticipated that approximately 350 patients will be required to enter the screening phase for 240 patients to be randomised into the treatment phase.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of new IIH by consensus criteria (see Section 16.2, Appendix 2), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Newly diagnosed patients with screening commenced no more than 4 weeks after the diagnostic LP
4. Lumbar puncture opening pressure ≥ 25 cm cerebrospinal fluid (CSF) at diagnosis
5. Presence of bilateral papilloedema (Frisén grade ≥1). Verification of papilloedema by the OCT Reading Centre. Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerves should be conducted for evaluation by the Independent Adjudication Committee (IAC)
6. Perimetric Mean Deviation (PMD) defined as between -2 to -7 decibels (dB) in at least one eye. Eyes meeting this criteria will be defined as ‘study eyes’

7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses, (reliability confirmed by the Visual Field Reading Centre) in study eyes
8. Two or more headache days over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period
9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.8, Appendix 8 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Able to provide written informed consent

5.2.2. Exclusion Criteria

Patients will not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusion criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth or seventh nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate (including if used as a migraine preventative),

diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)

6. 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

Vision related exclusion criteria:

7. Any disease other than refractive error that causes visual loss in the study eyes. Where there is uncertainly this would be determined by the Independent Adjudication Committee [IAC]
8. Refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in study eyes. In addition, participants with myopia of worse than -6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes. Where there is uncertainly this would be evaluated by the Independent Adjudication Committee [IAC]

Headache related exclusion criteria:

10. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

11. Untreated previously diagnosed obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
12. Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
13. COVID-19 vaccine within 2 weeks prior to screening
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which may affect the safety of the patient
16. History of drug-induced immune-mediated thrombocytopenia from exenatide products
17. Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2

18. Using any glucose-lowering medication
19. Currently taking warfarin
20. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)
21. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
22. Any of the following abnormalities in clinical laboratory tests at screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
23. Using recreational or illicit drugs at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
24. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period
25. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
26. Any contraindication to lumbar puncture procedure in the opinion of the investigator
27. Has participated in any other interventional trial within 1 month prior to the screening visit.
28. Is pregnant or breastfeeding

Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2

6. TRIAL ASSESSMENTS AND PROCEDURES

6.1. Procedures at Each Visit

Trial procedures and timings are presented in the Time and Events Table, Table 1.

No procedures should be performed prior to obtaining informed consent. All visits (except telephone call visits) should be performed at the clinic. Should a clinic visit not be possible, due to a patient self-isolating, the visit will be conducted at the earliest opportunity and will not constitute a protocol deviation.

6.1.1. Visit 1 Screening

The screening period must be a minimum of 7 days, up to a maximum of 10 days. Visit procedures can be performed in a single visit or over a number of visits during the screening period. Ideally all screening procedures should be performed on the same day.

- Obtain patient's written informed consent
- Eligibility criteria
    - Including confirmation that diagnostic LP occurred within the last 4 weeks with an opening pressure ≥ 25 cm CSF in lateral decubitus position
- Demographics (sex, age and ethnicity)
- Medical and ophthalmic history
- Concomitant mediation history
- Headache history (including family history of migraine (a first degree relative with and migraine) and headache in the 7 days prior to diagnostic LP)
- Headache preventative medication review
- Headache diary dispensed and diary training – to be performed on first day of screening.
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Height, body weight and BMI
- Full physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram

- Visual Assessments to both eyes
    - Frisén grading will be initially assessed by the site and then the presence of papilloedema verified by the OCT Reading Centre. Where there is uncertainty, fundus photos and or ultrasound scan (B scan) of the optic nerve may be conducted for evaluation by the IAC to confirm eligibility.
    - Optical coherence tomography imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard using a size III white stimulus)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay, and where there is uncertainty about eligibility this should be referred to the IAC.
    - Visual Acuity (LogMAR score)
- Laboratory assessments
- Trial medication training. Patients will be asked to self-administer 1 dose of placebo at the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable will be excluded

6.1.2. Visit 2 Baseline

- Review eligibility criteria
- Concomitant medications review
- Headache preventative medication review

- Review headache diary (Patient must meet required number of headache days as per inclusion criteria. If the headache diary exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit)
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse events review
- Targeted physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Visual Assessments to both eyes
    - Frisén grading will be assessed by the site
    - Optical coherence tomography imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
    - Visual Acuity (LogMAR score)
- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Laboratory assessments

- Anti-Drug Antibodies (ADA) blood sampling
- Patient randomised
- Trial medication training
- Trial medication dispensed and first dose self-administered at clinic. Patients will then be instructed to administer subsequent doses once weekly.
- Pharmacokinetic sampling (post-dose)

6.1.3. Visit 3 Telephone call

All patients will receive a telephone call at visit 3 to conduct headache preventative medication review, check for any AEs or changes in medication, procedures outside of protocol, health utilisation, to remind them to complete their diary and to answer any questions they may have on administration or storage of the trial medication.

6.1.4. Visits 4, 5, 6, 7, 8 and 9 Clinic visits

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI (not visit 4)
- Adverse event review
- Targeted physical examination (visit 6, 8 and 9 only)
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload processes to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.

- Humphrey Visual Field (24-2 SITA-Standard)
  - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
- Visual Acuity (LogMAR score)

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary (not visit 4)
- Health Utilisation Form
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-Drug Antibodies blood sampling
- Trial medication dispensing (not Visit 4) and accountability - patients should be reminded by the trial site to self-administer the trial medication weekly and to return used and unused trial medication at clinic visits

6.1.5. Visit 10

In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.

Where more than one dose has been missed during the 4 weeks preceding visit 10, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days.

- Concomitant medication review
- Headache preventative medication review
- Headache diary review

- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse event review
- Targeted physical examination
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
    - Visual Acuity (LogMAR score)
- Lumbar puncture (within 7 days of last dose of trial medication)
    - Lumbar puncture to be performed ideally after visual assessments
    - Performed in the lateral decubitus position according to LP SOP Appendix 1
    - In some cases the lumbar puncture might be conducted using imaging guidance according to the preference of the individual and site. This could be using x-rays, computer tomography or ultrasound guidance.

- If the procedure is not successfully performed it should be re-booked and repeated as soon as possible and the patient should remain on trial medication with the last dose within 7 days of the LP.

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Patient global impression of change question
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-drug antibodies blood sampling
- Trial medication accountability

Where it is not feasible to conduct all of visit 10 procedures on the same day, these could be split provided visual assessments are performed before the LP and the patient remains on trial medication with the last dose within 7 days of the LP.

6.1.6. Visit 11 Follow-Up

This visit will be performed as a telephone call to conduct headache preventative medication review and check for any AEs or changes in medication. In the event of any abnormal safety assessments identified at the end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments.

A urine pregnancy test (for women of childbearing potential) will be performed, this can be conducted at home if the visit is performed by telephone call.

6.1.7. Unscheduled visit for repeat visual assessments

Optional unscheduled visit for visual testing (HVF, OCT, LogMAR) for patients where there is concern about their visual decline or who perform inadequately or where there is technical failure (more than 15% false positive responses or inadequate performance indicated by the Visual Field Reading Centre for HVF; or OCT imaging not of satisfactory quality as determined by the OCT Reading Centre). Imaging only in the study eye(s).

- Optical coherence tomography Imaging

- Sites should initially check the scan quality. The OCT scan should go through the upload process to the OCT Reading Centre. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.

- Humphrey Visual Field (24-2 SITA-Standard)
  - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. Quality reports from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
- Visual Acuity (LogMAR score)

6.2. Trial Procedures

6.2.1. Screening Procedures

6.2.1.1. Demographics

The Investigator, or designee, should record the patient's sex, ethnicity, age, height, body weight and BMI at screening.

Ethnicity data will be collected in order to monitor any response differences in IIH disease progression/symptoms in different ethnicities.

6.2.1.2. Medical, Headache and Ophthalmic History

The Investigator, or designee, should record any ongoing co-morbidities and significant medical, headache and ophthalmic history along with the year in which such co-morbidities began (where known).

6.2.1.3. Reporting of Prior and Concomitant Medication

Concomitant treatment is any medication or therapeutic intervention being continued by the patient at trial entry and any new medication received during the trial. Prior treatment

includes previous medications, treatments and interventions received in the past but no longer ongoing.

For this trial, only relevant prior concomitant medications within the last 4 months will be recorded. These include:

- Treatment to lower ICP (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
- Headache preventative medication (including oral or botulism toxin A or monoclonal antibodies against CGRP or CGRP antagonists, or greater occipital nerve block)
- GLP-1 receptor agonist
- Warfarin
- Glucose lowering medication
- Recreational or illicit drugs

At every visit the Investigator or a qualified designee will ask the patient about relevant concomitant medication.

No new medication should be started during the trial, unless medically necessary. The patient should be advised to consult the Investigator or designee before taking any prescribed or over-the-counter medications. In the case of headache preventative medications or ICP lowering medications please see details in the rescue therapy section. Acute headache analgesics are permitted and should be reported in the diary.

6.2.2. Safety Procedures

6.2.2.1. Physical Examination

A full physical examination will be performed at the screening visit. At a minimum the following will be assessed: ear, nose and throat, cardiovascular system, pulmonary system, skin, abdomen and neurological system. At all other time points a targeted (symptom directed) examination will be performed at the Investigator's discretion.

6.2.2.2. Twelve- Lead Electrocardiogram

Twelve lead ECGs should be performed at the times outlined in the Time and Events table (Table 1) in a standardized manner, i.e., after the patient has rested in the semi-supine position for at least 10 minutes. Measurements will be made using an ECG

machine that automatically calculates the heart rate and measures PR, RR, QRS, and QT intervals.

All ECG traces will be reviewed and signed by the Investigator or designee and any abnormalities will be marked as clinically significant or not clinically significant.

6.2.2.3. Vital Signs

Vital signs, including systolic and diastolic blood pressure and heart rate, will be measured at the time points specified in Table 1.

Patients should rest in a supine position for 10 minutes before the vital signs are assessed. Three recordings will be taken and averaged.

6.2.2.4. Laboratory Assessments

Blood and urine samples will be processed at the site. Routine biochemistry and haematology samples will be evaluated at the trial appointed central laboratory. PK, ADA and CSF samples will be stored at the central laboratory and evaluated at a qualified international laboratory. Details of handling and shipping are described in the Laboratory Manual.

6.2.2.4.1. Haematology

Blood for the assessment of haematology parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Total blood count; consisting of:
  - Red blood cells
  - Haematocrit
  - Mean cell volume
  - Mean cell haemoglobin
  - Mean cell haemoglobin concentration
  - Glycated haemoglobin (HbA1C)
  - Blood glucose (non-fasting)
  - Platelets
  - White blood cells

- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Coagulation (prothrombin time, international normalised ratio, activated partial thromboplastin time, thrombin time, fibrinogen)
- Basophils

6.2.2.4.2. Clinical Chemistry

Blood for the assessment of clinical chemistry parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen
- Creatinine
- Total bilirubin
- Total protein
- Albumin
- Alanine transaminase
- Aspartate aminotransferase
- Alkaline phosphatase

6.2.2.4.3. Urinalysis

Urine samples will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed at each time point:

- Glucose
- Ketones

- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen

6.2.2.4.4. CSF

CSF sample from visit 10 LP will be retained for future potential analysis of disease and drug related biomarkers.

6.2.2.4.5. Pregnancy

At screening blood will be collected to enable a serum pregnancy test to be performed. At visits thereafter, urine will be collected from female patients of childbearing potential at the times outlined in the Time and Events table (Table 1) to enable highly sensitive urine-based pregnancy tests to be performed. Female patients who are identified as being pregnant during the trial will be withdrawn from further treatment but will continue to attend safety follow-up visits.

The Investigator or designee should report any pregnancies in female patients to the Sponsor or designee, using the Pregnancy Report Form, within 24 hours. The contact details for reporting are:

[redacted]

Female patients or partners of patients who become pregnant should be followed until delivery, stillbirth or termination. The outcome of the pregnancy and, if applicable, the health of the baby, should be reported to the Sponsor using the Pregnancy Report Form.

6.2.2.4.6. Pharmacokinetic sampling

Pharmacokinetic sampling is to characterize the pharmacokinetics of exenatide after once weekly subcutaneous administration of Presendin at the times outlined in the Time and Events table (Table 1).

The primary purpose of the pharmacokinetic sampling is to characterize the steady state concentrations of exenatide. All actual sampling times and dosing times will be recorded.

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.4.7. Anti-drug Antibodies sampling

Anti-drug antibodies sampling will be performed in all subjects at the times outlined in the Time and Events table (Table 1).

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.5. Adverse Events

Patients will be asked non-leading questions to assess how they are feeling at each clinic visit. Adverse events will be assessed and reported as outlined in Section 12.

6.3. Efficacy Procedures

6.3.1. Intracranial Pressure

Assessment of ICP will be measured by LP in the lateral decubitus position. The diagnostic LP is performed by the clinical team prior to recruitment and the measurement must be made from the lateral decubitus position. The research LP will be performed according to LP standard operating procedure (SOP), Appendix 1. Lumbar puncture will ideally be performed after visual assessments as outlined in the Time and Events table (Table 1).

In some cases the lumbar puncture might be conducted using imaging guidance according to the preference of the individual and site. This could be using x-rays, computer tomography or ultrasound guidance.

Any additional LP procedures, outside of the protocol would constitute a protocol deviation and ideally should be discussed with the Investigator before the procedure is performed.

Non-protocol LPs should be recorded in the Case Report Form.

6.3.2. Visual Assessments

Visual assessments should be performed on both eyes. All visual assessments should be uploaded without delay on the day of the visit to the OCT and Visual Field Reading Centres. In all cases the site is responsible for initial checks of the clinical data in the wider context of the patient's disease, as well as a data quality check.

6.3.2.1. Frisén grade

At Screening (visit 1) Frisén grading (0 – 5) should initially be performed at the site through a dilated pupil. The presence of papilloedema will be verified by the OCT

Reading Centre at screening (visit 1) and a report sent to the site. During screening, where there is uncertainty regarding the presence of papilloedema and / or Frisén grade a fundus photo and or ultrasound scan (B scan) of the optic nerve may be conducted (or may be requested by the OCT Reading Centre) and if uncertainty persists evaluated by the IAC.

At Baseline (visit 2) sites will reconfirm the Frisén grade

6.3.2.2. Optical Coherence Tomography

Imaging may be acquired using Heidelberg Engineering or Cirrus platforms according to the OCT SOP. Key measures are RNFL, optic nerve head size, and macular ganglion cell layer/complex thickness..

- Sites should initially check the clinical interpretation of the OCT scan and scan quality. The OCT should then go through the upload processes to the OCT Reading Centre. The OCT will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will then be sent to the site. Where the OCT is of insufficient quality, it should be repeated as soon as possible. Where the OCT has not been processed correctly at the site the processing should be re-performed as soon as possible thereafter. Repeated or reprocessed images would then be again transmitted to the OCT Reading Centre for a full assessment.
- If the site is concerned with the OCT findings, suggesting that the patient is a potential treatment failure and may require rescue therapy, the OCT Reading Centre review will be prioritised and when indicated expedited to the IAC.

6.3.2.3. Humphrey Visual Field

The visual field will be measured by Humphrey Visual Field analysis (24-2 SITA-Standard) including standardised refraction as indicated, according to the Visual Field Centre SOP (Manual of Procedures).

- At screening HVF will be reviewed by the Visual Field Reading Centre to confirm eligibility.
- Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in study eyes (including >15% false positives), is an exclusion criterion. HVF can be repeated to obtain as assessment with reliable performance.
- If the site is concerned with the HVF findings, suggesting that the patient is a treatment failure and may require rescue therapy, the Visual Field Reading Centre review will be prioritised and when indicated expedited to the IAC.

6.3.2.4. Visual Acuity

Assessment of visual acuity will be recorded using a LogMAR chart (unaided, best corrected, and with pin hole).

6.3.3. Headache Assessments

Patients will be provided with an electronic/paper diary at screening to complete during the trial. Information collected will be used to assess the following headache parameters:

- Monthly headache days
- Monthly moderate to severe headache days
- Responder rate
- Monthly acute analgesic use
- Headache severity (11-point NRS)

6.3.3.1. Headache Preventative Medication Review

A review of any headache preventative medications taken by the patient will be undertaken at each clinic visit. If the Investigator alters the headache preventative medication, this will be considered rescue medication (Section 10.1.1) and the IAC consulted. Use of headache preventative medication will be recorded at trial visits as outlined in the Time and Events table (Table 1).

Patients will record their acute headache analgesic use in their trial diary.

6.3.4. Patient Reported Outcomes

6.3.4.1. Visual related

Assessment of visual related quality of life will be derived from self-reported responses to the VFQ-25-10 item supp (see Section 16.6 Appendix 6).

6.3.4.2. Health-related

Assessment of health-related quality of life will be derived from self-reported responses using the following questionnaires:

- 36-item short form survey
- EuroQol -5 dimension -5 level survey

A Healthcare Utilisation Form will be completed by the trial site staff at clinic visits.

All questionnaires can be found in Section 16, Appendix 3 for SF-36 and Appendix 4 for the EuroQoL- 5D-5L survey.

6.3.4.3. Headache related Quality of Life

Assessment of headache-related quality of life will be derived from self-reported responses to the Headache Impact Test-6 questionnaire and performed at time points as outlined in the Time and Events table (Table 1). A copy of this questionnaire can be found in Section 16.5, Appendix 5.

6.3.4.4. Patient Global Impression of Change

The Patient Global Impression of Change will be conducted at visit 10, as outlined in the Time and Events table (Table 1).

It is a single item questionnaire using a seven-point verbal response scale to assess overall change in the patient's status since taking trial medication. A copy of this questionnaire can be found in Section 16.7, Appendix 7

6.3.5. Body Weight and Body Mass Index

The patient's body weight and BMI will be measured at the time points as outlined in the Time and Events table (Table 1).

The patient's height will be measured at Screening (shoes off).

7. SAFETY MEASURES DUE TO A GLOBAL CRISIS

The COVID-19 global pandemic presents numerous challenges to the conduct of ongoing clinical trials. In line with the FDA and European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (EMA, 2021), the following protocol considerations are provided to ensure patients safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain. Other unforeseen global crises may occur during the conduct of the study, similar to the COVID-19 global pandemic, in which case the following protocol considerations may also be applied.

Recognizing the flexibility required to manage the impact of the pandemic (or other global crisis) on this clinical study, additional details will be added to respective study manuals, project plan documents, and communicated to the investigative sites as needed. For any additional questions, the investigator should confer with the sponsor.

Number of Trial Patients

The evolving situation of the pandemic (or other global crisis) may result in a substantial number of patients' early withdrawal from the study, which could affect the data integrity of the study. Because of this risk, the sponsor may decide to recruit additional patients in the study, beyond the expected number, to mitigate such risk.

Study Visits

There are a number of on-site visits that would be required to ensure study validity. If there are local travel restrictions, isolation requirements, or the investigator determines it to be unsafe for patients to attend their scheduled study visits, the site staff may conduct certain visits via telemedicine (phone or video calls) to minimize patient risk as follows.

Screening Period

The following visit must be performed in person:

- Screening/Visit 1
  Note: To minimize direct, in-person contact between site personnel and patients, certain screening procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site.
  Specifically, the following procedures may be done remotely:
  - Informed consent (where applicable, per approved IRB/IEC process)
  - Demography

- Medical and ophthalmic history
- Concomitant medication history
- Headache history
- Headache preventative medication review
- Train and dispense headache diary
- Trial medication training

Randomised period

- Baseline (Visit 2)
  There are essential aspects to the baseline visit which must be performed in person.
  If the baseline visit is delayed the headache diary should utilise the preceding 7 days data. Where the visit is delayed by more than 10 days due to a global crisis the patient will be considered to have failed screening. Patients who screen failed due to the pandemic (or other global crisis) may be rescreened at a later time, if feasible.

  To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:
  - Concomitant medication review
  - Headache preventative medication review
  - Headache diary review
  - Adverse events
  - Patient reported outcomes
  - Health utilisation form

- Visit 4, 5, 6, 7, and 8
  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination

- Urine pregnancy test
- Electrocardiogram
- Optical coherence tomography imaging
- Humphrey Visual Field
- Visual acuity testing
- Laboratory assessments
- Pharmacokinetic sampling
- Anti-drug antibodies sampling

To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Adverse events
- Patient reported outcomes
- Health utilisation form

- Visit 10

  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination
  - Urine pregnancy test
  - Electrocardiogram
  - Optical coherence tomography imaging
  - Humphrey Visual Field
  - Visual acuity testing
  - Laboratory assessments
  - Pharmacokinetic sampling
  - Anti-drug antibodies sampling

- Lumbar puncture*

* Lumbar puncture to be ideally performed after visual assessments. In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days, if possible, but this can be extended according to local government policy if a patient is unable to attend (for example if a patient is self-isolating) as long as medication use is maintained as above.

- Follow up/ Visit 11

  This should be performed as a telephone visit unless clinical contact is necessary, as per protocol. Where face to face contact is required, this should be conducted at the earliest available opportunity.

Study Drug Dispensation and Distribution

If a patient is not able to attend a clinic visit, to ensure the continuity of providing patients' study drug within the constraints imposed by the pandemic (or other global crisis), the site staff may decide to supply study drug to patient as follows:

- Adequate supplies of study drug can be shipped to the patient by the study staff using a third-party service with approval from the patient. The third-party vendor will be agreed upon with the sponsor.
- The patient may request, with prior arrangement/agreement with the site, an authorized individual (a relative or delegate) to retrieve the study drug from the study site if the patient is unable to personally to do so.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (e.g., phone

calls, emails, video visits) with the sites to get information on study progress, patient status, and information on issue resolution as detailed in the Data Monitoring Guidelines, Remote source data verification.

If the trial site monitor cannot be on-site to carry out the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be carried out by a pharmacist from the site pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the site pharmacy directly, or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts with Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of patient for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

Clinic visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as the crisis-related limitations permit.

All safety data that are possible to obtain locally should be collected at a remote visit. These measurements may include the use of local practitioners and resources.

Exceptional measures taken in response to a crisis (e.g., COVID-19) and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3 guidance.

8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

Patients will receive lifestyle advice as per routine care from their treating physician.

9. INVESTIGATIONAL PRODUCT

9.1. Dosage and Administration

9.1.1. Randomised Period

During the 24-week randomised treatment period (Figure 1) patients will be randomised in a 1:1 ratio to receive active treatment or placebo.

Either

Presendin (2.0mg exenatide) as a SC injection, self-administered once weekly.

Presendin is supplied as 2 parts, one vial consisting of a drug part (white or grayish white powder in a clear vial) and one pre-filled syringe containing the diluent part (colourless liquid). The drug part is suspended in the diluent part solution and administered as a suspension.

or

Placebo as a SC injection, self-administered once weekly.

Placebo is supplied as 2 parts (visually identical to the Presendin vial and pre-filled diluent syringe). The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. The drug part is suspended in the diluent part solution and administered as a suspension.

9.2. Dose Rationale

The proposed 2mg weekly dose was based on the pharmacokinetic performance of the Peptron formulation (PT320). Pharmacokinetic profiles obtained after repeated once weekly dosing of 2mg of PT320 s.c. (as specified in the Presendin IB phase 2 clinical study in patients with type 2 diabetes) were comparable to those predicted by the population PK model developed for weekly s.c. administration of the recommended dose of the 2mg Bydureon extended-release formulation [Cirincione 2017],with time to reach the steady state slightly shorter for PT320 than for Bydureon (7-8 weeks vs 8-10 weeks) and with steady state plasma concentrations remaining within a comparable range for both products. Based on the same molecule and dose, comparable plasma concentrations for PT320 and Bydureon and the established safety profile of Bydureon a similarly acceptable safety and tolerability profile for PT320 is expected.

9.3. Maintaining the Blind

This is a double-blind trial.

A computer/website system will be used to maintain the blind for this trial. The site will be provided with website login details for the system. If the Investigator needs to unblind a patient's treatment, due to a medical emergency, the website should be accessed to unblind for that patient. .

The responsibility to break the treatment code in emergency situations resides solely with the investigator.

9.4. Treatment Assignment

Patients will be randomised in a ratio of 1:1 to receive active treatment (Presendin) or placebo. A computer/website system will be used to randomly assign each patient to a treatment arm.

9.5. Packaging and Labelling

Individual supplies of trial medication will be provided to the sites in a double-blind format. The labels will contain all information required to meet the applicable local regulatory requirements.

Further information on packaging, labelling and dispensing are included in the Pharmacy Manual.

9.6. Preparation

Each dose of trial medication is provided as two parts, a single use vial and a pre-filled syringe of diluent. Patients will receive training and be provided with an instruction sheet with details, on how to store, prepare, self-administer and discard/keep used trial medication.

9.7. Handling and Storage

Presendin, the active trial medication, contains the active ingredient, exenatide, which is hygroscopic and light sensitive and must be protected from light during storage. Prior to use, all trial medication should be stored refrigerated at 2-8ºC.

9.8. Product Accountability and Assessment of Compliance

In accordance with International Council of Harmonisation – Good Clinical Practice (ICH-GCP), each trial centre will account for all supplies of trial medication. Details of receipt, storage, assembly, and return will be recorded. The unit of accountability will be one single active or placebo vial. Needles will be disposed of in a sharps box.

All unused supplies will either be destroyed or returned to the trial Sponsor at the end of the trial in accordance with instruction by the Sponsor.

All trial medication will be self-administered by the patients. If a dose is not administered as planned, patients will record the missed dose in their electronic/paper diaries and it will be documented in the electronic case report form (eCRF).

9.9. Treatment of Investigational Product Overdose

Definition of Overdose: More than 1 (one) dose in 24 hours.

In the event a patient overdoses on trial medication the Investigator should be notified as soon as possible. If symptoms appear, the Investigator will treat the patient according to their clinical judgement depending on the type of clinical signs and symptoms exhibited by the patient. The Sponsor should be notified in writing within 24 hours of the Investigator becoming aware.

Effects of overdose that may be seen include severe nausea, severe vomiting and rapidly declining blood glucose concentrations.

9.10. Occupational Safety

There are no known occupational safety risks to staff. The Material Safety Data Sheet will be made available where required by local regulations.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

10.1. Recording Prior and Concomitant Medication

All relevant medication taken within 4 months of screening should be recorded in the eCRF along with all relevant medication taken from the start of the screening period until the final follow-up visit (Section 6.2.1.3).

At a minimum the following information will be collected:

- Generic name
- Dose
- Frequency
- Date started
- If ongoing (or if not, then the date stopped will be recorded)
- Reason for taking the medication

10.1.1. Treatment Failure

Rescue therapy can be initiated when there is a treatment failure. Since perimetric variability increases with increasing visual field damage, a two-tiered approach is used [Wall, 2013].

10.1.1.1. Possible treatment failure

Possible treatment failure is defined as those with baseline PMD between -2 and -3.5dB who experience a decline of > or equal to 2dB. In those with a baseline PMD between -3.5 and -7 dB, those who experience a decline of > or equal to 3 dB.

When a possible treatment failure is identified, perimetry, and if needed, other visual tests, should be repeated at an unscheduled visit.

10.1.1.2. Definite treatment failure

A definite treatment failure occurs when a patient with baseline PMD between -2 and -3.5dB experiences a decline of > or equal to 2dB which remains after repeat perimetry. Or in those with a baseline PMD between -3.5 and -7 dB who experience a decline of > or equal to 3 dB which remains after repeat perimetry.

These cases should be reviewed without delayby the IAC (who will review all visual and clinical data) to confirm or refute a definite treatment failure.

10.1.2. Rescue Therapy/Rescue Intervention for Progressive Visual Loss

When a treatment failure occurs, rescue therapy can be initiated, in addition to study treatment, based on the medical judgement of the Investigator. Decisions should always be discussed with the IAC without delay and if possible before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to be a medical emergency. In all cases the final decision lies with the Investigator.

Patients showing progressive visual loss will be considered for rescue therapy with acetazolamide or an alternative diuretic. In cases where the visual loss is severe and “rapid”, and believed by the Investigator to necessitate surgical intervention, the intervention will be conducted in accordance with local emergency practice.

10.1.2.1. Rescue Therapy for Headache

If the Investigator wishes to alter the headache preventative medication (any drug can be considered), this decision should always be discussed with the IAC before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to

be a medical emergency. Use of headache preventative medication will be recorded at trial visits.

Use of acute headache analgesics is not considered as rescue medication and is permitted but must be documented in the headache diary (monthly analgesic use).

10.2. Prohibited Medications

10.2.1. Prior to screening and randomisation

- Treatment to lower ICP within 1 week prior to screening (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed).
- Exposure to fluoroquinolones, lithium, vitamin A, or tetracyclines within 2 months of diagnostic LP
- Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
- Warfarin
- Glucose-lowering medicationCOVID-19 vaccine within 2 weeks prior to screening
- Recreational or illicit drugs during screening period

  Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2.

10.2.2. During the trial

- Treatment to lower ICP (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed). These will all be considered rescue medication (Section 10.1.2) and the IAC consulted. Use will be considered a protocol deviation.
- If the Investigator alters the headache preventative medication (including oral or botulism toxin A or monoclonal antibodies against CGRP or CGRP antagonists, or greater occipital nerve block) this will be considered headache rescue medication (Section 10.1.2) and the IAC consulted.
- Glucagon like peptide-1 receptor agonists
- Recreational or illicit drugs
- Warfarin
- Glucose-lowering medication
- Regarding COVID-19 vaccination, the risks of receiving or not receiving the vaccination have been considered in relation to the IMP and no additional risks are envisaged. Hence patients may choose to have or not have COVID-19 vaccination or booster during this trial.

The investigator should follow the cautions and guidance on the management of other concomitant medication or DDIs as detailed in section 9.2.5.2 (Drug-Drug Interactions) of the IB.

11. PATIENT COMPLETION AND WITHDRAWAL

11.1. Patient Completion

Patients will be classed as having completed the trial once they have completed all required trial visits. See Section 11.2.1 for early discontinuations.

11.2. Patient Withdrawal

11.2.1. Patient Withdrawal from Trial Treatment

A patient will be withdrawn from treatment for any of the following reasons:

- Withdrawal of consent to continue in the trial. The reason for this will be documented if provided
- The Investigator or Sponsor, for any reason, decides the patient should be withdrawn from the treatment
- Lack of compliance with the trial medication is classified as <75% or >125% of scheduled doses over the course of the trial, excluding supply issues
- Adverse events, which cannot be tolerated by the patient
- Pregnancy during the treatment period

Patients will be encouraged to continue in the trial to the end of the randomised treatment period even if they stop trial medication so that data can be collected for the Intention-To-Treat (ITT) population.

If a patient is withdrawn from treatment during the randomised treatment period, they will be encouraged to return for all trial visits up to visit 10. If a patient does not want to return then at a minimum they should be encouraged to attend for visit 11 procedures as a safety follow-up visit.

11.3. Treatment after the End of the Trial

Patients will not be provided with trial medication following the end of the trial.

11.4. Screen and Baseline Failures

Information will be collected on all patients who sign the Informed Consent Form (ICF).

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

12.1.1. Causal Relationship

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration

along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

- Probable relationship: event occurs in a plausible time relationship to the medication administration and cannot be explained by concurrent disease or other drugs or chemicals; the response to the withdrawal of the drug should be clinically plausible
- Possible relationship: event occurs with a reasonable time sequence to the medication administration, but could also be explained by concurrent disease or other drugs or chemicals; information on the drug withdrawal may be lacking or unclear
- Unlikely relationship: event occurs with little temporal relationship to the medication administration and other factors such as drugs, chemicals or underlying disease provide plausible explanations
- Not related: event has no temporal relationship to the medication administration or there is a definite alternative aetiology

12.1.2. Severity Criteria

An assessment of severity grade will be made using the following categorical descriptors:

- Grade 1 means a relatively minor side effect
- Grade 2 means a moderate side-effect
- Grade 3 means a severe or medically significant but not immediately life-threatening side-effect
- Grade 4 means life-threatening consequences
- Grade 5 death related to AE

The exact definition of each number in the scale depends on the particular side effect according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [CTCAE].

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g., laboratory abnormalities).

Adverse events occurring as a result of LP should be specifically recorded. Occurrence of post lumbar headache will be specifically reported.

12.1.3. Reporting Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of

the patient's final safety follow-up visit. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol. Adverse events reported after dosing will be classed as treatment emergent AEs.

All AEs, regardless of seriousness, severity, or presumed relationship to trial therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the source documents and the eCRF their opinion concerning the relationship of the AE to trial therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

The patient must be provided, on the first day of trial medication (Day 1), with a "patient card" indicating the following:

- Patient number
- Name of the investigational product
- Investigator's name and 24-hour contact information
- Statement that the patient is participating in a clinical trial

12.2. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Deterioration of IIH necessitating CSF shunting or optic nerve sheath fenestration or dural venous sinus stenting will be recorded as an SAE and reported.

Deterioration of IIH necessitating hospital admission will be recorded as an SAE and reported.

Pre-defined exclusions:

- Hospitalisation for unrelated elective procedures
- Post LP headache

12.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to the trial medication and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator Brochure) and serious.

12.2.2. Expected Adverse Events

Perceived deterioration of IIH necessitating attendance or admission to hospital will not be reported as an SAE, but these events will be reported and recorded at follow-up. Non-protocol LPs will be reported at follow-up.

12.2.3. Reporting Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor designee (contract research organisation) within 24 hours of their knowledge of the event.

SAEs will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's final safety follow-up visit.

Information regarding SAEs will be transmitted to the Sponsor's safety contact using the SAE Form, which must be completed and signed by the Investigator, and transmitted to the Sponsor's safety contact within 24 hours.

The contact details are:

[redacted]

The Sponsor assumes responsibility for appropriate reporting of SAEs or SUSARs to the regulatory authorities. The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee (IEC) that approved the protocol unless otherwise required and documented by the IEC.

An annual safety report will be submitted to the Institutional Review Board once a year via the Investigator.

12.3. Reporting and Handling of Pregnancies

Pregnant patients will be withdrawn from the trial.

Female patients will be instructed to notify the Investigator immediately if they become pregnant during the trial and up to 12 weeks after discontinuation/completion of trial medication. Pregnant patients will be withdrawn from further trial treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the trial.

A pregnancy as such is not an AE, unless there is a possibility that the trial medication has interfered with the efficiency of any contraceptive measures. The Investigator should report all pregnancies to the Sponsor contact or designee within 24 hours of being informed of them. The pregnancy report form should be used instead of the SAE form.

The pregnant patients will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

Patients will give consent on enrolment that the Investigator will report any pregnancy to the Sponsor and that further information will be collected until delivery.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalised prior to database lock providing detailed methods for the analyses outlined below.

13.1. Hypotheses

This trial compares outcomes in IIH patients under Presendin and matched placebo. The primary hypothesis that will be tested is:

- The ICP measurement in the Presendin group is equal to the ICP measurement in the placebo group at Week 24; against the alternative that the outcomes differ

13.2. Trial Design Considerations

13.2.1. Sample Size Assumptions

The target sample size for the trial is 240 randomised patients, i.e., 120 patients per arm. We justify this figure in the following sections. The two outcomes for which we sought to power the study are ICP and PMD.

13.2.1.1. Intracranial Pressure Power

The most difficult parameters to specify for a sample size calculation pertain to the variability of outcomes. We present a brief summary of the literature. Baseline standard deviations (SD) of ICP in previous trials were: 5.4 (n=10) and 6.3 (n=17) in the Drug Trial [Markey, 2017]; 5.0 (n=16) (data on file); and 5.7 (n=32) and 5.3 (n=30) in the Weight Trial [Ottridge, 2017]. Post-baseline standard deviations were slightly lower (and less than 6.0) in three of these five arms; and increased slightly in one (but remained less than 6.0). The post-baseline standard deviation however increased to over 8.0 in the surgery arm of the Weight Trial because the surgical intervention dramatically impacted ICP in some patients. In the NORDIC trial [Wall, 2014] however, the standard deviation of baseline ICP was much higher, at 9.4 in the treatment arm (n=86). Seeking to avoid underpowering the study, we elected to proceed with the SD estimate for the NORDIC trial as this is the most similar trial population to the planned IIH EVOLVE trial (both recruiting acute IIH). We assume that control arm baseline and 24-week ICP SD equals 9.4, Presendin baseline ICP SD equals 9.4, and Presendin 24-week ICP SD equals 10.4. These values assume the variability of ICP measures in untreated patients is as high as has been seen in the NORDIC trial and assumes that the variability in treated patients is slightly higher still. We anticipate that the standard deviation will be slightly higher in the experimental arm as treatment effects will potentially manifest changes in ICP. However, we do not expect such variability to be as inflated in this trial relative to control as it was

in the Weight Trial because of the likely difference in treatment effect between surgical and drug interventions.

Under this parameterisation, when testing for a difference between arms at 24-weeks of 5 CSF (justified below) using a total sample size of 240, assuming that up to 50% of observations are missing (i.e. 60 final LPs are completed in each arm), using a 5% significance level by Analysis of Covariance (ANCOVA) adjusted for baseline ICP, the two stratification variables, and treatment arm, we expect to have approximately 85% power. If 40% of observations are missing (i.e. 72 final LPs are completed in each arm), we expect power to be 91%. These figures have been inferred by computer simulation. Of the 165 patients in IIHTT [Wall, 2014] it was reported that "only 85 participants (47 [55%] in the [treated] group and 38 [48%] in the placebo group) agreed to a lumbar puncture at month 6."

We expect a high rate of missing data because lumbar puncture is an invasive procedure that patients can find painful and traumatising [Scotton, 2018]. If patients have an unpleasant experience at the diagnostic LP they are also more likely to decline the LP at trial outcome. If patients do decline the final LP, logically it will be because of the baseline experience rather than their prevailing ICP. If data for the LP at 24 weeks is missing, the reason will be recorded.

Outcomes from previous trials show that baseline and post-baseline distributions of ICP show central tendency with approximate symmetry, so we conclude that normality is a reasonable assumption and therefore ANCOVA is a defensible analysis method.

13.2.1.1. Perimetric Mean Deviation Power

We summarise here the estimated power for detecting differences between arms in the PMD outcome measure. In the NORDIC trial [Wall, 2014], the authors observed that the improvement from baseline to 6-months in PMD was 0.71dB greater in the experimental arm than the control arm. Cross-sectional SD of PMD was 1.1-1.2 at baseline. Table 2 in their publication shows that the standard error of mean PMD is higher at 6m than at baseline, likely reflecting a combined effect of missing data at 6-months and greater variability of post-baseline measures. We plan to take repeated measures of PMD at baseline, 2 weeks, 1-month (m), 2m, 3 m, 4m, 5m and 6m. Assuming that the overall SD of PMD scores is 1.8, thus introducing some reasonable inflation on Wall *et al.*'s baseline variability parameter for the reasons identified, using the formula given on p.31 of Diggle, Liang & Zeger (1994) we would expect to require 142 patients in total to detect a difference of 0.71dB (justified below) with 90% power at a 5% significance level, if the serial correlation between repeated measures is 0.4 (and we expect a value in this region) [Diggle, 1994]. If the serial correlation parameter is as low as 0.3, the required sample size increases to 166.

Note that the method used above assumes full follow-up and data collection. Although every effort will be made to collect all outcomes, naturally some missing data is expected. If we inflate the maximum sample size identified above by up to 30% to account for some data loss, we require up to 166 / 0.7 = 237 patients. The assumed 30% missing data rate was adjudged to be realistic by the Sponsor based on previous trials in IIH. Thus, we expect to be able to cover the impact of missing data using the extra patients necessitated by the sample size calculation for ICP.

The above assumes only one eye is measured per patient. In actuality, some patients may provide outcomes for both eyes because any eye that satisfies the eligibility criteria (see Section 5.2) will be enlisted in the study. Put another way, all patients will provide outcomes in at least one eye, and some will provide outcomes in two. Second eyes will naturally be highly correlated with first eyes. From a sample size perspective, this means the additional information in second eyes will be of modest value. Nevertheless, outcomes on second eyes will contain some additional information and should be included in the analysis in the interest of efficiency. When estimating sample size, for the sake of simplicity and because of uncertainty in the rate of eligibility in second eyes, we have assumed that each patient yields outcomes from only one eye. Eligible second eyes will be included in the analysis with appropriate model terms to handle the within-patient correlation (further details are included in the SAP). As such we expect outcomes from second eyes to provide a modest uplift in power to the scenarios presented here.

This section assumes a longitudinal analysis method such as hierarchical regression.

13.2.2. Stratification

At the outset, it is expected that markers of disease severity will be prognostic of potential efficacy. For this reason, it is proposed to stratify randomisation by, baseline ICP (<35cm or ≥35 cm), baseline body mass index (< 30 kg/m^2 or ≥30 kg/m^2) and baseline PMD (worse than or equal to -3.5dB or better than -3.5dB).

13.2.3. Sample Size Sensitivity

13.2.3.1. Clinically Meaningful Effect Sizes

Minimally relevant effect sizes have not been fully determined in IIH given it is a rare disease with relatively few previous trials.

The ICP diagnostic threshold in IIH is 25 cm CSF [Mollan, 2018]. However, it is not necessary to reduce ICP <25 cm CSF to achieve remission from signs and symptoms of IIH in all patients [Sinclair, 2010]. The clinical importance of a particular change in ICP

will vary depending on the starting ICP and the impact this pressure has on vision and headache. Changes in ICP of 5 cm CSF are generally considered meaningful when treating IIH patients. For example, in a clinical study evaluating the benefits of weight loss in IIH patients, a 16.5% (6.2 cm CSF) reduction in ICP resulted in a statistically significant improvement in headache and vision measures as well as quality of life [Sinclair, 2010]. In the IIH Treatment trail (n=165), a study evaluating the drug treatment acetazolamide against placebo, a reduction of -5.9 cm CSF was seen in association with significant improvement in PMD, OCT measures of papilloedema and quality of life measures [Wall, 2014].

The minimally clinically important change in the perimetric mean deviation adopted into clinical practice was stablished by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) group and the IIH Treatment Trial (IIHTT). The investigators found a 0.71dB difference in the PMD between the two trial arms (comparing acetazolamide with placebo) that was clinically meaningful. The change of 0.71dB was interpreted as clinically meaningful as this was accompanied by significant changes in LP opening pressure, papilloedema (measured by OCT), general quality of life and visual related quality of life [Wall, 2014, Bruce, 2016].

The clinically meaningful effect size for MHD reflects that for a phenotypically similar headache, chronic migraine. Recent randomised trials in patients with chronic migraine [Tepper, 2017; Silberstein, 2017], episodic migraine [Goadsby, 2017], or both [Camporeale, 2018] have shown in post-baseline months 1–3, odds of migraine relative to baseline of 0.5–0.8 with placebo and 0.5–0.3 with experimental drugs. Decreases in MHD relative to baseline grew in time, and placebo responses were stronger in chronic migraine than episodic migraine. In the three placebo-controlled, blinded trials, these equated to odds-ratios of migraine compared with placebo of 0.8–0.6, or absolute differences of 1.5–2.5 MHD [Sinclair, 2010; Tepper 2017; Silberstein, 2017; Goadsby, 2017].

13.2.4. Trial Stopping Criteria

There are no trial-specific stopping rules.

13.3. Data Analysis Considerations

13.3.1. Estimands

We have specified intercurrent events that are material to the measurement of our primary and secondary outcomes, and unbiased estimation of treatment effects attributable to Presendin.

ICP-lowering medication include: acetazolamide, topiramate, diuretics, glucocorticoids (oral dexamethasone and oral prednisolone). Headache-preventative medications include: amitriptyline, topiramate, nortriptyline, beta blockers, candesartan, sodium valproate, pizotifen, botox, CGRP-therapy.

13.3.1.1. Outcome: Intracranial pressure (ICP)

13.3.1.1.1. Intercurrent event: ICP-lowering medications

All patients are expected to have elevated ICP because it is a defining characteristic of the disease. ICP is a physiological variable that is unlikely to show spontaneous improvement without treatment. For these reasons, we expect ICP-lowering medication use to be greater in the placebo arm. If a patient takes medication that is intended to reduce their ICP, it is logical to expect that their ICP will be reduced. Outcomes from patients that take ICP-lowering medications will confound the estimation of the causal treatment effect of Presendin. We have no data to estimate the length of effects of ICP-lowering medications. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have used ICP-lowering medications and replace these observations with arm-specific imputations. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin. Patients will consent at enrolment to forgo the use of ICP-lowering medications and be informed that taking ICP-lowering medications during the trial would constitute rescue therapy and a treatment failure and be a protocol deviation.

13.3.1.1.2. Intercurrent event: Off-protocol lumbar punctures

Lumbar punctures are commonly conducted to reduce intracranial pressure [Weisberg, 1977; Johnston, 1981; De Simone, 2005]. In some centres, they are given routinely although this has now been advised against in the International IIH Guidelines (Soler, 1998; Mollan, 2018). As such, they remain a material therapeutic option. LP is expected to reduce ICP mean opening pressure 32 (28-37) cm CSF to 19 (17-21) cm CSF post LP [Yiangou, 2019]. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify change in ICP after an LP, it is expected that effects in the majority of change would have dissipated completely within two months [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have had an off-protocol LP within

two months of the protocol-scheduled 24-week LP and replace these observations with arm-specific imputations. Where patients require off-protocol LP this would be a protocol deviation.

13.3.1.1.3. Inter-current event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in ICP [Sinclair, 2010]., Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure and replace with arm-specific imputations. Patients will be ineligible for the trial if they have had a surgical weight-loss procedure within 3 months of randomisation or fail to confirm that they do not intend to undertake such a procedure during the trial. They will also be informed at enrolment that undergoing a surgical weight-loss procedure would be a protocol deviation.

13.3.1.2. Outcome: Perimetric Mean Deviation (PMD)

13.3.1.2.1. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication (rescue medication due to treatment failure), it is logical to expect that their ICP will decrease and that papilloedema will reduce as a result, allowing visual fields to improve. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the PMD outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.2.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilloedema, allowing visual fields to improve. Patients that have LPs are expected to experience less pressure on the optic nerve, less papilloedema, and have better chances of

their visual fields improving. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilloedema after an LP the consensus of clinicians would predict that effects of the LP on papilloedema and therefore visual fields would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. PMD outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove PMD outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.2.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including improvements in visual fields [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove PMD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.3. Outcome: Papilloedema measured by OCT (optic nerve head size, retinal nerve fibre layer)

13.3.1.3.1. Intercurrent event: ICP-lowering medications

All patients will suffer from papilloedema at enrolment as it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that the papilloedema will reduce in turn. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the OCT outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.3.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the

associated symptoms of the disease, including reducing pressure on the optic nerve and papilloedema. Patients that have LPs are expected to experience less pressure on the optic nerve and therefore relatively less papilloedema. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilloedema after an LP the consensus of clinicians would predict that effects of the LP on papilloedema would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. OCT outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove OCT outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.3.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in papilloedema [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove OCT outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4. Outcome: Monthly headache days (MHD)

13.3.1.4.1. Intercurrent event: Headache-preventative medications

The great majority of patients are expected to suffer from headache because it is a common symptom of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes medication that is intended to prevent headache, it is logical to expect that their headache burden will be decreased. Despite the widely-observed short-term placebo-effect observed in headache outcomes, we expect headache-preventative medication use to be greater in the placebo arm. Outcomes from patients that take headache-preventative medications will confound the estimation of the causal treatment effect of Presendin (more so with botulinum toxin A and CGRP therapies). For these reasons, we propose to remove the headache outcomes following the administration of headache-preventative medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin. Patients who require a change to their headache preventative medications will do this through consultation with the IAC and such a change would be regarded as headache rescue therapy.

13.3.1.4.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing the frequency and intensity of headache. Beneficial effects dissipate with time. Prospective data documents alterations in headache for at least 7 days and whilst there is no prospective longitudinal data over a longer time period consensus amongst clinicians would widely acknowledge that headache in some individuals can be influenced for up to a month [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. MHD outcomes will be recorded daily via diaries. For the reasons stated, we propose to remove MHD outcomes recorded in the 4-weeks following each off-protocol LP and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in headache frequency and severity [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove MHD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.4. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that headache will reduce as a result. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the MHD outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.5. Primary Estimand (Hypothetical assuming no concurrent procedures, irrespective of adherence to treatment)

The primary estimand is defined as the following for the primary endpoint:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect ICP.

The primary estimand for the initial secondary endpoint will be handled similarly to the primary endpoint using the "Hypothetical" approach. The initial secondary endpoint is defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect PMD.

13.3.1.6. Secondary Estimand (Hypothetical)

The secondary estimand for the primary endpoint is defined as follows:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect ICP.

The secondary estimand for the initial secondary endpoint will be defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect PMD.

All details will be defined in the SAP.

13.3.2. Analysis Populations

The following analysis populations are planned for this trial:

- **Safety Population:** The Safety population includes all patients randomised to treatment who receive at least one dose of trial medication. This will be the population used for all safety analyses unless otherwise specified.
- **Intent-To-Treat Population (ITT):** The ITT population includes all patients randomised to treatment. This will be the main population for all efficacy analyses unless otherwise specified.
- **Per Protocol (PP)**: The PP population includes all patients randomised to treatment without important non-evaluable protocol deviations. Only protocol deviations with the potential to affect the trial results significantly, or to invalidate the interpretation of the data obtained, will lead to exclusion of patients from the PP population. Protocol deviations to be considered will include (but will not be limited to):
    - Failure to meet inclusion/exclusion criteria
    - Wrong treatment or incorrect volume of drug administration
    - Prohibited concomitant medications
    - Compliance of less than 75% or>125% with trial drug administration
    - Use of rescue procedures, including, off-protocol LPs, LP shunts or bariatric surgery

Assignment of patients to populations will be confirmed at a blinded data review meeting to be held before the trial database is locked.

If a patient is randomised incorrectly or is administered the incorrect trial medication, analyses of the ITT will be based on the assigned treatment, whereas all other analyses will be based on the actual treatment received.

13.3.3. Treatment Comparisons

Treatment comparisons will be undertaken between active and control groups. The primary outcome will be analysed as described in Section 13.2.1.

13.3.4. Safety Analyses

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, and ECG results.

All safety analyses will be performed on the Safety population.

13.3.4.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary (the most recent version before starting the trial will be used).

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

The number and percentage of patients reporting TEAEs, grouped by MedDRA system organ class and preferred term will be tabulated by treatment group. Summaries will be presented for all TEAEs, TEAEs by severity and TEAEs by relationship to trial medication.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged. The observation period in which an AE started will also be provided.

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed by trial arm. Treatment failures will be displayed by trial arm.

13.3.4.2. Clinical Laboratory Evaluations

Laboratory test results for each biochemistry and haematology parameter will be summarized descriptively by treatment group and time point as both observed values and change from baseline values.

The number of patients with clinical laboratory (biochemistry, haematology, and urinalysis) values categorized as below, within, or above the normal ranges (or as either normal or abnormal for urinalysis variables that do not have quantitative ranges), will be tabulated in relation to baseline (shift tables), for each clinical laboratory analyte by treatment group and time point.

Laboratory values will be displayed in the data listings and those that are outside the reference ranges will be flagged, along with corresponding normal ranges. Any patients with any markedly abnormal laboratory results will also be provided in a listing.

Pregnancy test results including reason, if not performed, will be listed.

13.3.4.3. Vital Signs and Body Mass Index Evaluations

Descriptive summaries of observed values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure and heart rate by treatment group and time point.

Body mass index will be derived at Screening, Baseline and Weeks 4, 8, 16, 24, 32 and 48 using height captured at Screening and weight at the respective assessment. Body mass index and weight will be summarized descriptively by treatment group and time point as both observed values and change from baseline values for Safety and ITT populations.

13.3.4.4. Electrocardiogram

Descriptive statistics of observed values and change from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected according to Fridericia's formula (QTcF). These summaries will be presented by treatment and time point for the Safety population.

The number and percentage of patients with values beyond clinically important limits will be summarised including those with an increase in QTcF >30 msec increase from baseline and >60 msec increase from baseline or those with an absolute QTcF value of >450 msec (male patients) or >470 msec (female patients).

13.3.4.1. Other Safety Evaluations

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed by trial arm.

13.3.5. Patient Reported Outcomes Analyses

All patient reported outcome endpoints (VFQ-25, HIT-6, SF-36, EQ-5D-5L) will be analysed as observed and presented with change from baseline in a descriptive summary of treatment and visit

The number and percentages of PGIC responses will be tabulated by treatment and visit.

13.3.6. Missing Data

Although every effort will be made to collect responses from all patients at all scheduled time points, there undoubtedly will be some missing data. The SAP describes in detail steps for dealing with missing data using relevant imputation strategies for specific endpoints that adjust for treatment arm, centre, baseline value, and stratification variables.

13.3.7. Reporting Deviations from the Statistical Plan

Any deviations from the planned analyses will be described and justified in the final clinical trial report.

14. TRIAL ADMINISTRATION

14.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Before initiation of a trial site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the trial in accordance with ICH-GCP and applicable country-specific regulatory requirements.

The trial will be conducted in accordance with all applicable regulatory requirements.

The trial will be conducted in accordance with the EU Clinical Trial Regulation 536/2014, ICH-GCP, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- An IEC/Institutional Review Board review and approval of trial protocol and any subsequent amendments and all ICFs or other information given to the patient
- Patient informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each patient before participation in the trial. Written informed consent will be collected following a review of the patient's information leaflet by the potential patient and a discussion between the patient and the Investigator or suitably qualified designee.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this trial. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site(s) by an outside authority before the Inspectors are permitted access to any of the trial records or the trial areas.

14.2. Trial Monitoring

In accordance with applicable regulations, ICH-GCP, the monitoring plan and the Sponsor's and/or delegate procedures, monitors will contact the site before the start of the trial to review with the site staff the protocol, trial requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data

collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The Sponsor and or delegated monitors will perform risk-based monitoring during the conduct of the trial to ensure that:

- The data are authentic, accurate and complete
- The patient's safety and rights are being protected
- The trial is conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP and all applicable regulatory requirements

14.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all relevant documents.

14.2.2. Data Handling and Record Keeping

Following closure of the trial, the Investigator or head of the medical institution (where applicable) must maintain all site trial records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor SOPs and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of

ownership of the records in the event that the Investigator is no longer associated with the site.

14.3. Provision of Trial Results and Information to Investigators and Publications

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical trial report. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete trial results at a mutually agreeable location.

The Sponsor will also provide the Investigator with the full summary of the trial results. The Investigator is encouraged to share the summary results with the trial patients, as appropriate.

If the Sponsor decides to publish the results, then they will provide the Investigator with an opportunity to review the manuscript. If the Investigator wishes to publish anything related to the trial, then they must provide the Sponsor with the draft publication and allow them no less than 14 days to review the document. The Investigator cannot publish without written authorisation from the Sponsor.

14.4. Data Management

For this trial, patient data will be collected using an eCRF and combined with data provided from other sources in a validated data system. Patient's identifiable data (e.g., name, initials, address etc.) will not be collected in the eCRF or transferred to Invex Therapeutics. Clinical data management will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the statistical analysis or the credibility of the Clinical Study Report. Original CRFs will be retained by Invex Therapeutics; the Investigator will also retain a copy.

Management of clinical data will be performed in accordance with the applicable Sponsor standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Affairs and World Health Organisation Drug dictionary.

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)

b. Maintain SOPs for using these systems

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)

d. Maintain a security system that prevents unauthorised access to the data

e. Maintain a list of the individuals who are authorised to make data changes

f. Maintain adequate backup of the data

g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)

Training on the use of the electronic data collection system will be provided to all relevant trial site staff.

14.5. Independent Adjudication Committee

The IAC will consist of international medical experts in neurology or ophthalmology who are independent of the Sponsor team.

The role of the IAC will be:

- To support the Investigators with opinions on the eligibility of potential patients
- To provide opinions regarding treatment failure and need for rescue medications required during the trial

Further details on the composition, activities and responsibilities of the IAC can be found in the IAC charter.

14.6. Data Safety Monitoring Committee

Details on the composition, activities and responsibilities of the DSMC can be found in the DSMC charter.

14.7. Insurance, Indemnity and Finance

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this trial against future claims by trial patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all trial procedures have been carried out according to this protocol.

The financial aspects of the trial are addressed in a separate agreement.

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16. APPENDICES PROVIDED FOR TRIAL INVEX-CLIN-IIH-301

16.1. Appendix 1: LP SOP

Diagnostic lumber puncture

The diagnostic lumbar puncture (LP) is performed by the site as part of routine care to confirm the diagnosis of Idiopathic Intracranial Hypertension (IIH). This is not a research LP. For the patient to be eligible for the IIH Evolve trial the diagnostic LP must have the opening pressure measured in the lateral decubitus position in line with the guidance below. The LP must be within 4 weeks of commencing screening.

Research lumbar puncture

A research LP is performed at the end of the Randomised Period/ Week 24/ Visit 10. This is the primary outcome for the trial. In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10.

Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days. We recommend that the LP should be performed after visual assessment.

The LP should be performed by a trained clinician or health care professional according to local standard of care. The only mandatory requirement for the trial is that the measurement of LP opening pressure is conducted as per below.

Procedure

Suggested equipment required:

- Antiseptic cleaned trolley;
- Cleaning solution (Iodine or chlorhexidine)
- 2 pairs of sterile gloves;
- Sterile wound pack;
- Lumbar puncture manometer (up to 3 should be available) with corresponding 3 way valve stopcocks (should be included in pack);

- Needle point 20 gauge lumbar puncture needle;
- 10ml syringe x 1;
- Green syringe needle, blue syringe needle and orange syringe needle;
- Gauze pads x 1;
- 3 sterile universal pots;
- Sterile dressing.

Suggested technique

For a standard (non-image guided) LP:

- Ask the participant to lie in the lateral left position; they should be relaxed.
- The legs must be flexed at the hip at a 90˚ angle (support may be need to maintain this position).
- The L3/4 intervertebral space should be located using anatomical landmarks (the midline between the posterior superior iliac crests). If this is difficult, consider using ultrasound to identify the correct structures: IV space and spinous processes of L3 and L4. The space above or below may also be accessed if needed.
- Mark the location of needle entry.
- Clean a large circumference around the needle entry site using 70% alcohol or chlorhexidine using a sterile technique.
- Infiltrate 1-2% lidocaine subcutaneously and into the vertebral ligaments. Aspirate prior to infiltration to avoid intravascular injection. No more than 3mg/kg should be infiltrated (1% contains 10mg per 1ml).
- Once the area is appropriately anaesthetised, insert the needle bevel up, horizontally to the marked area and towards the umbilicus.
- Once a ‘give’ is felt, withdraw the stylet and ensure flow of CSF.

LP opening pressure measurement (mandatory)

- Pressure readings MUST be taken with the patient lying in the lateral left (or right) decubitus position.
- Connect the manometer and record the opening pressure:
    - If the patient’s thighs are compressing their abdomen then very slowly extend the legs at the hip joint to ensure the abdomen is not compressed.
    - Ensure the patient is not speaking or breath holding (avoid valsalva)

- Allow time (sometimes around 5 minutes), for the pressure to become consistent (small fluctuations in the pressure with respiration should be seen) before a reading is taken

- Collect a sample of CSF in sterile universal container (size typically 25-30ml), and collect a 3ml CSF sample for the research trial. This should immediately be stood upright in a wet ice bath until processing. Process should be within 30 minutes of collection (see the Laboratory manual).
- There is no need to record a closing pressure for the trial.
- Replace the stylet, withdraw the needle and place a sterile dressing over the area.

For an image guided-LP:

This may be performed using guidance by ultrasound, x-ray or computerised tomography (CT). This should be performed by a suitability qualified health care professional (e.g. radiologist). The positioning for a patients undergoing an image guided LP vary internationally. For this trial the initial position for an image guided LP can be according to local expertise but the LP pressure measurement MUST be conducted in the lateral decubitus position as described above. This ensures standardisation across the trial.

Post procedure advice:

This should be in line with local hospital care pathways. We would suggest:

- Lie flat for approximately 30 minutes (there is no evidence to support that lying flat for any duration reduces a post LP headache). Pragmatic advice on mobilisation when the patient has recovered is advised.
- Simple analgesia may be prescribed and dispensed for post-procedure pain (headaches or back pain);
- Oral fluids may help with post-procedure headache (non-evidenced based recommendation).
- Remind the participant of the possible adverse effects.

16.2. Appendix 2: IIH Diagnostic criteria [Mollan, 2018]

A. Papilloedema

B. Normal neurological examination (except sixth cranial nerve palsy)

C. Neuroimaging: normal brain parenchyma (no hydrocephalus, mass, structural lesion or meningeal enhancement). Venous thrombosis excluded in all.

D. Normal CSF constituents (less than or equal to 7 white cells per mm^3 with normal protein and glucose

E. Elevated lumbar puncture pressure ≥ 25cm CSF

16.3. Appendix 3: 36-item short from survey

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

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Santa Monica, California 90401-3208

16.4. Appendix 4: EuroQol -5 dimension-5 level survey

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

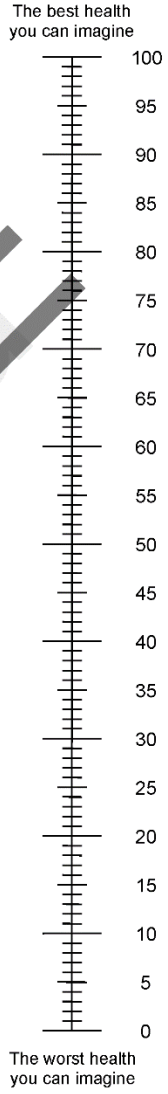
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



16.5. Appendix 5: Headache Impact Test-6

HIT-6™
(VERSION 1.1)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1	When you have headaches, how often is the pain severe?	Never	Rarely	Sometimes	Very Often	Always
2	How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?	Never	Rarely	Sometimes	Very Often	Always
3	When you have a headache, how often do you wish you could lie down?	Never	Rarely	Sometimes	Very Often	Always
4	In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
5	In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
6	In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?	Never	Rarely	Sometimes	Very Often	Always

COLUMN 1 (6 points each)	+	COLUMN 2 (8 points each)	+	COLUMN 3 (10 points each)	+	COLUMN 4 (11 points each)	+	COLUMN 5 (13 points each)

To score, add points for answers in each column.
Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36-78.

HEADACHE IMPACT TEST™

What Does Your Score Mean?

If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your doctor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

About HIT

The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36®* health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

SF-36® is a registered trademark of Medical Outcomes Trust and John E. Ware, Jr.

16.6. Appendix 6: Visual Function Questionnaire-25 & 10-item Supplement

PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

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7/29/96

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don't apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your overall health is:**

(Circle One)

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. **At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

(Circle One)

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

15. Are you currently driving, at least once in a while?

(Circle One)

Yes..... 1 *Skip To Q 15c*

No 2

15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have

(Circle One)

No difficulty at all 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty..... 4

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0 1 2 3 4 5 6 7 8 9 10

Worst Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0 1 2 3 4 5 6 7 8 9 10

Worst Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognising people you know from across a room?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

10-ITEM NEURO-OPHTHALMIC SUPPLEMENT TO THE NEI-VFQ-25

The following are additional questions and statements about problems that involve your vision or feelings you may have about your vision condition. After each question, there will be a list of possible answers. Please choose the response that best describes your situation.

Please answer all questions as if you were wearing your glasses or contact lenses (if any). Please take as much time as you need to answer each question.

1. How much difficulty do you have performing tasks when your eyes are tired?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

2. Because of your vision, how much difficulty do you have identifying objects or performing tasks in bright sunlight?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

3. Because of your vision, how much difficulty do you have parking a car?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

4. Because of your vision, how much difficulty do you have using a computer?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

For each of the following statements, please indicate if it is definitely true, mostly true, mostly false, or definitely false for you or if you are not sure.

5. I have a feeling that my two eyes see differently, even with correction (glasses or contact lenses).
(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

6. I have a feeling that my eye or eyelid appearance is unusual.

(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

For each of the following, please indicate if it is true for you all, most, some, a little, or none of the time.

7. My vision is blurry, not clear, or "fuzzy."

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

8. I have trouble focusing on or following moving objects.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

9. I have double vision with both eyes open that is not present when either eye is covered.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

10. My eyelid(s) droop.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

16.7. Appendix 7: Patient Global Impression of Change

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is

✓*one box only:*

[1] ☐ Very much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very much Worse

16.8. Appendix 8: Contraception

Birth control methods which may be considered as highly effective (that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods).

Patients should be instructed not to take their oral contraceptive within 1 hour prior to administration of trial medication.

Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [1]
- sexual abstinence [2]

[1.] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant.

[2.] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Study Number: INVEX-CLIN-IIH-301 Protocol	Compound No.: Presendin Version: 3.0

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

Effective Date: 08-Jun-2022

Short Title: A Phase III trial to determine the efficacy and safety of Presendin in IIH – IIH EVOLVE

Abstract: Idiopathic intracranial hypertension (IIH) has significant associated morbidity and reduced quality of life. There is a significant risk of visual loss and patients also typically suffer with chronic disabling headaches.

This trial has been designed to evaluate the efficacy and safety of a new release formulation of exenatide (Presendin) in the reduction of intracranial pressure (ICP) in patients with IIH. The primary outcome will be determined by change in ICP, as measured by lumbar puncture (LP).

Eligible, consenting patients will be randomised in a ratio of 1:1 to receive Presendin or placebo as a weekly dose for 24 weeks.

Author	Department	Company
Emma de Launay	Clinical Operations	Invex Therapeutics Ltd.

Invex Therapeutics

[redacted]

SPONSOR SIGNATURE PAGE

Sponsor Signatory:

A Sinclair — 9.6.2022

Doctor Alexandra Sinclair
MBChB, PhD, FRCP

Date

Chief Scientific Officer

Invex Therapeutics Ltd.

[redacted]

SPONSOR INFORMATION PAGE

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Sponsor Contact Information:

Invex Therapeutics Ltd
[redacted]

INVESTIGATOR SIGNATURE PAGE

I, the undersigned, have read and understood the protocol and am aware of my responsibilities as an Investigator. I agree to conduct the study in accordance with this protocol, the Trial Reference Manual and any subsequent amendments, the Declaration of Helsinki, ICH GCP guidelines, and the laws and regulations of the country in which the study is being conducted.

Investigator Name and Qualifications: _____

_____ _____

Investigator Signature Date

[Investigator Affiliation]

INVESTIGATOR INFORMATION PAGE

Details will be provided in the Investigator Site File

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ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCRF	Electronic Case Report Form
BMI	Body Mass Index
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DGM	Data-Generating Models
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
GCL	Ganglion Cell Layer
GLP-1	Glucagon Like Peptide-1
HVF	Humphrey Visual Field
ICF	Informed Consent Form
ICP	Intracranial Pressure
IAC	Independent Adjudication Committee
ICH-GCP	International Council of Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
IIH	Idiopathic Intracranial Hypertension
ITT	Intention-to-Treat
LP	Lumbar Puncture
MAR	Missing At Random
MD	Mean Deviation
MHD	Monthly Headache Days
NRS	Numeric Rating Scale
OCT	Optical Coherence Tomography
PK	Pharmacokinetic
PP	Per Protocol
QTcF	QT Interval corrected according to Fridericia's formula
RNFL	Retinal Nerve Fibre Layer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	36-item short form survey
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event

ULN	Upper Limit of Normal
VFQ-25-10 item	Visual Function Questionnaire-25 and 10-item supplement

PROTOCOL SUMMARY

Rationale

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends.

IIH has significant associated morbidity and reduced quality of life. Elevated ICP causes papilloedema universally at disease onset and can lead to permanent visual loss. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Besides risk of visual loss, the most disabling aspect for patients is severe chronic headaches driven by elevated ICP. Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but the failure rates are high and frequent complications and side effects occur.

A modified release formulation of exenatide (Presendin) has been developed and this trial has been designed to evaluate the efficacy and safety of Presendin in IIH. The modified release formulation has been chosen to enable a once weekly dosing.

Objectives

Primary Objective

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

The baseline LP is the diagnostic LP.

Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation (PMD) as measured by the Humphrey Visual Field analyser (24-2 SITA (Swedish Interactive Testing Algorithm)-Standard)
- Papilloedema as measured by optical coherence tomography imaging (retinal nerve fibre layer (RNFL) thickness and optic nerve head volume measurements)

- Monthly headache days (MHD)
- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

Safety Objectives

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

Exploratory Objectives

To determine the effect of Presendin on:

- Macular ganglion cell layer/complex thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes (PROs)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Endpoints

Primary Endpoint

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

The baseline LP is the diagnostic LP.

Secondary Endpoints

- Perimetric Mean Deviation
- Retinal nerve fibre layer thickness
- Optic nerve head size
- The number of monthly headache days (MHD). Monthly headache days will include 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 require acute headache analgesia.
- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs)
- Resting 12-lead ECG
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

Exploratory Endpoints

- Macular ganglion cell layer/complex thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes:
  - Visual Function Questionnaire-25 and 10-item supplement (VFQ-25-10 item supp)
  - Headache Impact Test -6 (HIT-6)
  - 36-item short from survey (SF-36)
  - EuroQol -5 dimension -5 level (EQ-5D-5L) survey
  - Patient Global Impression of Change (PGIC)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Trial Design

This is a randomised, placebo-controlled, double-blind, multi-centre trial requiring 240 adult randomised patients with IIH to determine the efficacy and safety of Presendin.

Consenting patients with a diagnosis of IIH will enter a 1-week screening period, in which there will be no investigational treatment, to gather baseline measurements and to check eligibility. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period due to the real risk of visual loss. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Wall, 2014, Markey, 2017 and Mollan, 2021]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

At the screening visit, patients will be provided with training on the self-administration of the trial medication and provided with a leaflet to take home. Patients will be asked to self-administer one (1) dose of placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed a screen failure and will not be randomised into the trial. Eligible patients will then be randomised to receive either Presendin or matching placebo for 24 weeks in

a 1:1 ratio. After completion of the randomisation period patients will have an end of treatment clinic visit. Five weeks after the end of treatment visit, an end of trial safety follow up telephone visit will also be performed.

The duration of the double-blind treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy over a 3-month time horizon. Additionally, an alternative off label drug used in IIH (acetazolamide) evaluated efficacy over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk. The duration of the trial for each patient will be up to 30 weeks, which includes a 1-week screening period, a 24-week randomised double-blind treatment period, and a treatment follow-up period of 5 weeks.

Trial Population

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of new IIH by consensus criteria (see Section 16.1, Appendix 1), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Newly diagnosed patients with screening commenced no more than 4 weeks after the diagnostic LP
4. Lumbar puncture opening pressure ≥ 25 cm cerebrospinal fluid (CSF) at diagnosis
5. Presence of bilateral papilloedema (Frisén grade ≥1). Verification of papilloedema by the OCT Reading Centre. Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerves should be conducted for evaluation by the Independent Adjudication Committee (IAC)
6. Perimetric Mean Deviation (PMD) defined as between -2 to -7 decibels (dB) in at least one eye. Eyes meeting this criteria will defined as ‘study eyes’
7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses, (reliability confirmed by the Visual Field Reading Centre) in study eyes
8. Two or more headache days over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period

9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.7, Appendix 7 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Able to provide written informed consent

Patients must not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusion criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth or seventh nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
6. 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

Vision related exclusion criteria:

7. Any disease other than refractive error that causes visual loss in the study eyes. Where there is uncertainly this would be determined by the Independent Adjudication Committee [IAC]
8. Refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in study eyes. In addition, participants with myopia of worse than -6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes. Where there is uncertainly this would be evaluated by the Independent Adjudication Committee [IAC]

Headache related exclusion criteria:

10. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

11. Untreated previously diagnosed obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
12. Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
13. COVID-19 vaccine within 2 weeks prior to screening
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which may affect the safety of the patient
16. Using any glucose-lowering medication
17. Currently taking warfarin
18. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)
19. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)

20. Any of the following abnormalities in clinical laboratory tests at screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
21. Using recreational or illicit drugs at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
22. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period
23. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
24. Any contraindication to lumbar puncture procedure in the opinion of the investigator
25. Has participated in any other interventional trial within 1 month prior to the screening visit.
26. Is pregnant or breastfeeding

Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2

Trial Assessments

Table 1: Time and Events

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		+3	± 1	± 3	± 3	± 5	± 5	± 5	± 5	± 14		± 5
Month	0	0			1	2	3	4	5	6		
Week	-1	0		2	4	8	12	16	20	24		29
Day	-7	1	3	15	29	57	85	113	141	169		204
Informed consent	X											
Inclusion/Exclusion criteria	X	X (review)										
Demography (sex, age, ethnicity)	X											
Medical & Ophthalmic History	X											
Concomitant medication history	X											
Headache history	X											
Concomitant medication review		X	X	X	X	X	X	X	X	X		X
Headache preventative medication review	X	X	X	X	X	X	X	X	X	X		X
Train and dispense headache diary	X											
Review headache diary[1]		X	X	X	X	X	X	X	X	X		
Vital signs[2]	X	X		X	X	X	X	X	X	X		(X)
Height	X											

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Body weight and BMI	X	X			X	X	X	X	X	X		
Adverse Events[15]		X	X	X	X	X	X	X	X	X		X
Physical Examination (T = targeted)	X (Full)	X (T)				X (T)		X (T)	X(T)	X (T)		(X)
Pregnancy Test[3]	X (Serum)	X		X	X	X	X	X	X	X		X
Electrocardiogram	X	X		X	X	X	X	X	X	X		(X)
OCT Imaging	X	X		X	X	X	X	X	X	X	X	
Assessment of Papilloedema Frisén grade[4]	X	X										
Perimetry	X	X		X	X	X	X	X	X	X	X	
Visual Acuity Testing (LogMAR score)	X	X		X	X	X	X	X	X	X	x	
Patient Reported Outcomes (HIT-6, SF-36, EQ-5D-5L, VFQ-25 & 10-item supp)		X			X	X	X	X	X	X		
Health Utilisation Form		X	X	X	X	X	X	X	X	X		
PGIC assessment										X		
Laboratory assessments[5]	X	X		X	X	X	X	X	X	X		(X)

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**29**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**204**
Pharmacokinetic (PK) sampling[6]		X[7]		X	X	X	X	X	X	X		
Anti-Drug Antibodies (ADA) sampling		X		X	X	X	X	X	X	X		
Lumbar Puncture[8]										X[9]		
Trial medication training[10]	X	X										
Randomisation		X										
Trial medication Dispensing	X	X			X	X	X	X	X			
Trial medication Accountability				X	X	X	X	X	X	X		

1 The screening period must be a minimum of 7 days, up to a maximum of 10 days. Patients who do not meet the eligibility criteria based on diary review at randomisation/baseline (e.g., too few headache days or unacceptable concomitant medication use) will be considered screen failures; however, if the patient wishes and the Investigator is in agreement, he/she can be re-screened as a new patient. If the screening period exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit. Trial site research team should review diaries remotely on a weekly basis to ensure compliance and follow up any patients with missing data

2 Vital signs to include: blood pressure and heart rate

3 Women of child-bearing potential. Serum pregnancy test to be conducted at screening, thereafter, highly sensitive urine pregnancy tests will be conducted. Visit 11 urine pregnancy test may be conducted at home

4 Frisén grade will be evaluated locally and the presence of papilloedema verified by the OCT Reading Centre at screening to confirm eligibility. Indeterminate cases should be referred to the IAC (and supplemented with fundus photography and ultrasound scan of the optic nerve) to confirm papilloedema prior to randomisation visit

5 Haematology, coagulation, biochemistry and urinalysis

6 All actual sampling times and dosing times will be recorded

7 Baseline Post-dose PK blood sample

[8] The diagnostic LP will be the baseline LP and must be performed in lateral decubitus position. Patients with ICP <25 cm CSF at diagnosis will be excluded

[9] Lumbar puncture to be performed after visual assessment. CSF sample from visit 10 LP will be retained for future potential analysis

[10] Patients will be provided with training on the self-administration of the trial medication. The patient will be asked to self-administer placebo at visit 1 to demonstrate ability to self-inject. Patients who are not comfortable to self-inject will be excluded

[11] If patients discontinue in the randomised double-blind treatment period they will be encouraged to return for all trial visits up to visit 11. If a patient does not want to return for all visits then they will be asked to return at a minimum for visit 11 procedures for safety follow up

[12] In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days

[13] Optional unscheduled visit for visual testing (HVF, OCT, LogMAR) for patients in whom there is concern about visual decline or who perform inadequately or where there is technical failure (more than 15% false positive responses or inadequate performance indicated by the Visual Field Reading Centre for HVF; or OCT imaging not of satisfactory quality as determined by the OCT Reading Centre)

[14] In the event of any abnormal safety assessments identified at end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments

[15] Reporting of AEs/SAEs will continue up to the final follow up visit 11

1. INTRODUCTION

1.1. Background and Rational

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends [Mollan, 2019a]. There is a high rate of repeat hospital admission in IIH (increased by 446% in last decade), reflected in escalating healthcare costs (in England £462 million/year predicted by 2030 [Mollan, 2019a] and more than $444 million in the USA [Friesner, 2011]).

The cause of IIH is not fully understood. Recent research suggests that IIH is a disease of systemic metabolic dysregulation characterised by central adiposity [Hornby, 2017], double the risk of cardiovascular disease in excess to that mediated by obesity [Adderley, 2019] and dysfunctional adipocyte metabolism primed for weight gain [Westgate, 2021]. Patients are also insulin resistant and have a unique hormone signature of androgen excess both systemically and in the cerebrospinal fluid.[O'Reilly, 2019]

Morbidity in IIH is due to the elevated intracranial pressure which can cause severe papilloedema (swelling of the optic nerve) which can ultimately lead to blindness. The risk of permanent visual loss is a major concern in IIH. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Headache is an additional major disabler and affects the majority of IIH patients (over 90%) [Yri, 2014; Markey, 2016; Mulla 2015] in the long term. Headaches significantly reducing quality of life [Mulla, 2015; Digre, 2015] are driven by raised intracranial pressure and often have a migraine- like phenotype (> 90%) [Mollan 2021a].

Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. [Piper, 2015; Mollan, 2018; Hoffmann, 2018]. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but there is a high failure rate and frequent complications. The lack of licenced or targeted treatments in IIH perpetuates poor outcomes for patients. A priority setting exercise was run by patients with IIH (James Lind methodology) [Mollan, 2019c] establishing effective therapy was the top priority from the patient group.

This trial will investigate an alternative therapeutic option for lowering ICP and thereby reducing papilloedema and consequently reducing the risk of visual loss. By reducing ICP it would also aim to improve headache, improving overall patient quality of life in IIH [Mollan 2021a].

Gut neuropeptides are increasingly being recognised for their role in the central nervous system (CNS). A principal gut neuropeptide is glucagon like peptide-1 (GLP-1), which is known to stimulate insulin release, proliferation of pancreatic beta cells and control of glucose regulation in diabetes [Campbell, 2013]. Exenatide is a GLP-1 receptor agonist. It has also been shown to have some actions in the CNS; GLP-1 is involved in regulating satiety and weight through signalling at the hypothalamus [Astrup, 2009]. There is also evidence that GLP-1 may have a role in fluid secretion. In the renal proximal tubule GLP-1 acts to reduce sodium resorption to promote diuresis [Gutzwiller, 2004; Websky, 2014]. The choroid plexus is the fluid secreting structure within the brain producing the majority of CSF. The structure of the choroid plexus epithelial cells is analogous to an inverted renal proximal tubule with a similar mechanism of secretion and hence GLP-1 receptor agonists may also reduce CSF secretion in the brain, leading to a decrease in ICP in patients with IIH.

Exenatide as well as other GLP-1 receptor agonists can lead to weight loss. In diabetic patients, weight loss of 2.8 - 4.4 kg has been reported over 6 months [Di Dalmazi 2020; Pujante 2012]. Whilst in non-diabetic overweight and obese patients exenatide caused sufficient weight loss between 2.0 – 5.1 kg [Moreno 2012]. In overweight and obese patients with polycystic ovarian syndrome exenatide led to 2kg more weight loss compared to placebo in over 12 weeks [Liu 2017]. Weight loss with exenatide therapy is increased in the setting of calorie restriction [Rosenstock 2010]. Weight loss is a desirable effect of exenatide as weight loss is therapeutic in IIH. Changes in body weight will be monitored during the trial and the impact on outcomes measures evaluated.

Exenatide is the active ingredient in Byetta, an immediate-release (IR) formulation and Bydureon, an extended-release (ER) formulation. These have been licenced for use in adults with type-2 diabetes since 2005 and 2014, respectively. Therefore, there is a wealth of available safety data from both clinical trials and real-world experience. Exenatide has been identified as a potential candidate for the treatment of neurological conditions involving raised ICP and a polylactic-co-glycolic acid (PLGA) ER exenatide formulation under the name Presendin, has been developed by Invex Therapeutics for the treatment of IIH.

Byetta has a known issue of rapid elimination of the product when given to humans, and because of this it needs to be administered twice daily to achieve its pharmacological effects. The data on file from the IIH Pressure trial has shown that in patients with IIH, exenatide administered twice daily was well tolerated and produced a positive effect on reducing CSF pressure. However, it is considered that the immediate release formulation of exenatide is not ideal for treating patients with IIH on a long-term basis. Presendin has been developed as an extended release formulation to allow for a reduction in dosing frequency to once weekly and more consistent therapeutic plasma levels.

This trial is designed to investigate the efficacy and safety of a modified release formulation of exenatide (Presendin) in patients with IIH.

Intracranial pressure

IIH is a debilitating condition characterised by raised ICP, which is clinically measured by LP [Mollan, 2018]. The units for measurement of LP are cm CSF and cm H_2O and these should be thought of as interchangeable and reflect the measurement of the height of the CSF column at LP. The measurement must be taken in the lateral decubitus position. Lumbar puncture is conducted to make a diagnosis of IIH. Lumbar puncture may be conducted in a clinical setting during the disease course to both monitor and treat the condition. Frequent therapeutic LPs are no longer recommended by the International IIH guidelines [Mollan, 2018]. This is because LP can be traumatic for patients and can occasionally cause significant complications (meningitis, spinal haematoma, pain) [Wright, 2012]. Hence, unnecessary LP's should be avoided. In some patients LP can alter other outcome measures, including measurements of papilloedema and headache [Yiangou, 2019]. Hence ideally, LP should be performed after these measures and symptoms have been assessed. Lumbar puncture can cause post-dural puncture headaches. The risk is 9-36% using a traumatic needle and 3-19% using an atraumatic needle [Wright, 2012]. Post-dural puncture headaches typically last less than a week but in some patients this can be longer [Yiangou, 2019]. Lumbar puncture pressure assessment of ICP reflects disease activity and is a useful and recognised outcome measure that has been utilised in other IIH trials [Markey 2020; Mollan 2021b].

Due to the invasive nature of LP, non-invasive measures of ICP are valuable. The majority of techniques historically evaluated as non-invasive surrogate measures of ICP lack sufficient quantification to be used clinically or in clinical trials. Optical coherence tomography (OCT) measures of the optic nerve have been shown to provide a useful surrogate measure to quantify changes in ICP [Vijay, 2020]. For example, at 12 months, Vijay *et al* showed that a change in optic nerve head height of 50 µ predicted a 5 cm CSF change in ICP [Vijay, 2020].

Visual Function

Perimetry is used to measure visual function in IIH clinical practice. This is assessed using a Humphrey Field Analyzer (program 24-2 SITA standard using a size III white stimulus) test. Patients are often unaware of their visual field loss until this becomes more severe and compromises daily activities. In patients with severe papilloedema optic atrophy can develop (measured objectively as loss of the macular ganglion cell layer on OCT imaging) and the loss of visual field becomes permanent. Patients at risk of rapidly progressive visual loss (also termed fulminant IIH) should receive emergency surgical intervention (most commonly a CSF shunt operation) [Mollan, 2018]. Patients requiring

emergency surgery will not be recruited into this trial. Medical therapy is used to treat those IIH patients not requiring emergency surgical intervention and will be included in this trial. But it is expected that approximately 5-10% will go on to need more aggressive intervention.

Measuring visual function with perimetry has a number of challenges in IIH which need to be carefully considered. The visual field test is dependent on technician and patient performance and can be prone to variability and inaccuracy [Cello, 2016; Wall, 2016]. Patients can perform poorly on automated perimetry [Cello, 2016], and there is a learning effect [Kutzko, 2000; Wall, 2016]. There are further confounding factors when considering interpretation of automated visual field testing in IIH. The high prevalence of functional vision loss, presenting as non-organic visual fields results in this disease, may bias trial outcomes [Kutzko, 2000; Ney, 2009]. Additionally, impaired executive function and attention deficits have been noted in IIH [Sørensen, 1986], and have been shown to impair performance of visual field testing in IIH [Grech, 2021].

The protocol has been designed with these challenges in mind and visual field testing performance will be assessed at trial entry and throughout with opportunity for repeated assessment if there is performance failure (a performance failure is defined as a substantial worsening of the perimetric mean deviation due to human factors rather than visual damage) [Cello, 2016].. The visual fields will be assessed by the Visual Field Reading Centre.

Papilloedema by change in optic nerve head size measured by OCT imaging.

Papilloedema is a reliable sign of raised ICP [Dunn, 2002]. Change in papilloedema has been used by all the randomised control trials in IIH to date to determine clinical improvement [Ball, 2011; Wall, 2014; Mollan 2021b]. Change in papilloedema has been graded by experts using the Frisén classification, although it is more reliably measured by OCT imaging [Ball, 2011; Wall, 2014]. Professional bodies and the literature endorse the use of OCT imaging for monitoring papilloedema in IIH [Mollan, 2018].

OCT imaging measures various aspects of the optic nerve. The retinal nerve fibre layer (RNFL) and optic nerve head volume are measurements that both reflect swelling of the optic nerve and hence the extent of papilloedema. Measures of macular volume can quantify the ganglion cell layer (GCL) thickness which reflects axonal loss. Optic nerve head measures on OCT correlate with visual field sensitivity loss [Salgarello, 2001]. Analysis has shown that OCT measures of the RNFL significantly reflect changes in visual field perimetric mean deviation (MD) (for every 10µm increase in RNFL there was associated with a 0.6dB decrease in MD) [Rebolleda, 2009]. Optical coherence tomography measures of the macula volume have been shown to predict axonal loss of the optic nerve [Albrecht, 2017]. Most importantly, ganglion cell volume has been shown

to significantly correlate with the Humphrey visual field MD [Vijay, 2020]. This indicates that the GCL can be measured to reflect visual function. In other neurological diseases OCT has also been found to measure neuronal loss and correlated with visual loss [Petzold, 2010]. In summary, OCT assessment of the optic nerve and GCL represent objective measures of papilloedema and optic nerve axons which reflects visual function.

The scan quality can be compromised if the automated software segmentation of the OCT is not accurate. This occurs particularly in those optic nerves with more pronounced papilloedema [Aojula, 2018]. Hence the quality and segmentation of all OCT scans will be assured by the OCT Reading Centre and scans will be repeated if of insufficient quality.

Headache

Headache is the predominant presenting feature in IIH [Mollan, 2019a]. Patient morbidity is high because of disabling headaches and they have been found to be the key driver for poor quality of life [Mulla, 2015; Digre, 2015]. Research into headache treatments were endorsed as clinically relevant by a priority setting partnership which included the opinions of the patients' carers and physicians [Mollan, 2019c].

It has been well documented that headache characteristics in IIH are typically migraine-like (up to 90%) [Mollan, 2019b; Mollan 2021a]. The headache location can be halo-cranial, frontal, temporal or parietal with features including nausea, throbbing pain, photophobia and phonophobia [Yri, 2015]. A Danish trial of 44 IIH patients noted that 82% of patients had migraine-like attacks [Yri, 2014]. A prospective trial in 52 IIH patients in the UK characterised 80% of headaches as migraine-like [Yiangou, 2019]. As reported by the Idiopathic Intracranial Hypertension Treatment Trial, US, the headache phenotype was recorded as migraine or probable migraine in 68% of 144 patients with active IIH [Friedman, 2017]. A retrospective trial in Iran in 68 IIH patients characterised migraine-like headaches in 63% [Sina, 2017]. Other headache characteristics are typically tension-type or unclassified [Mollan, 2019b].

Hence whilst IIH headaches are not diagnostically the same as migraine according to the International Classification of Headache Disorders, 3rd edition Beta, they are very similar in character [Olesen, 2018]. The International Headache Society core outcomes for migraine are therefore applicable to IIH headaches [Tassorelli, 2018].

Headache in active IIH is driven by ICP. This is evidenced by the fact that removal of CSF fluid results in improved headache severity. In a prospective cohort study, headache severity improved in 71% following a standardised LP [Yiangou, 2019]. Ninety-five percent of IIH patients had improvement in headache symptoms at 1 month following

shunt placement [Daou, 2020]. Weight loss leading to reduction in ICP also significantly reduced headache [Sinclair, 2010].

Medications that reduce ICP have been shown to modulate headache. In an open label trial using topiramate and acetazolamide, both of which are known to modulate ICP [Scotton, 2019], relief of headache was reported after a mean treatment period of 3.75 months in the topiramate group and 3.3 months in the acetazolamide group [Çelebisoy, 2007].

Importantly, headache measures (severity and monthly headache days) in IIH significantly correlate with changes in ICP [Mollan 2021a]. The IIH weight trial [Mollan, 2021b], a randomised controlled parallel group multicentre trial in the United Kingdom, investigates weight management methods in IIH. Participants with active IIH (evidenced by papilloedema) and a body mass index (BMI) $\geq 35 kg/m^2$ were recruited. The primary outcome was ICP as measured by LP opening pressure at 12 months, with secondary outcomes of ICP at 24 months and headache outcomes at 12 and 24 months. Headache severity was correlated with ICP at baseline; change in headache severity and monthly headache days correlated with change in ICP at 12 months. Importantly those with the greatest reduction in ICP over 12 months had the greatest reduction in headache frequency and severity. This implies that treatment of ICP should improve headache in IIH.

The following headache outcomes are clinically relevant and are recommended by the American Headache Society [American Headache Society] and International Headache Society to identify patients who are benefiting from treatments. Headache outcomes are derived from a 28-day diagnostic headache diary. This is used in clinical trials to prospectively collect daily information on headache occurrence, severity, associated symptoms, and use of acute analgesic medications.

Although a headache diary is typically over 28 days, for IIH headache it was felt unethical to have patients off treatment for this more prolonged period during screening due to the real risk of visual loss. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Mollan 2021b]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

Monthly headache days

Monthly headache days (MHD) will include 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 require acute headache analgesia. This is the most relevant and objective measure of headache.

Moderate to severe monthly headache days

A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications. This outcome captures the more disabling headaches.

Moderate to severe MHD was recently reported as the primary endpoint in a prospective open label study providing evaluation of the effectiveness of erenumab, a calcitonin gene-related peptide (CGRP) monoclonal antibody, to treat headaches in IIH patients [Yiangou, 2021]. It is also used to measure headache in other secondary headache conditions such as persistent post traumatic headache [Aojula 2018; Ashina, 2020].

Headache responder rate (≥50% reduction in MHD)

Headache responder rate (≥50% reduction in MHD) is the proportion of patients achieving at least 50% reduction in the mean number of MHD, of any intensity, from baseline to the defined trial end point. This criterion is clinically relevant as it is used as an empirical review for continuing or discontinuing headache therapy [Diener, 2020]. Responder rates can be used in meta-analyses of placebo controlled randomised controlled trials.

Headache responder rate (≥50% reduction in moderate to severe MHD)

Headache responder rate (≥50% reduction in moderate to severe MHD) is the proportion of patients achieving at least 50% reduction in the moderate to severe MHD from baseline to the defined trial end point. It is well recognized that 50% responder rates may not fully capture the benefits of treatment [Matharu, 2017]. For example, a patient may improve from a disabling 20 severe headache days per month to 11 moderate headache days per month. Despite this considerable clinical benefit, such a patient would not be considered a responder because headache days were not reduced by ≥50%, and as a result might lose access to beneficial treatment. Hence, responder rates of ≥30% are also important [Vernieri, 2019]. In IIH, a disorder of chronic severe headaches, a clinically meaningful treatment responder rate has not been definitively established, although the International Headache Society Clinical Trials Subcommittee has suggested the use of a ≥30% reduction from baseline for chronic migraine.

Headache severity

Headache severity is an important measure and impacts quality of life. It is vital to consider some treatments which benefit headache may not reduce the MHD but if the severity is markedly improved this will lead to great overall functional benefit to the

patient and is clinically relevant [Silberstein, 2008]. Recording the decrease in intensity is an indicator of reduced disability, which is clinically meaningful.

Monthly use of acute headache rescue medications

Use of acute headache analgesics reflects a judgement of the inefficacy of the test treatment; hence it is a helpful secondary outcome. In Sinclair *et al.* reduction in analgesic days was significant and associated with clinical remission of IIH [Sinclair, 2010]. Additionally, a high portion of IIH, up to 48% [Yiangou, 2021] have medication overuse and medication overuse headache, and reduction in analgesic days mitigates these. Reduction in monthly use of acute headache analgesic is an additional endpoint that contributes to clinically meaningful results.

Quality of life in IIH

IIH has a detrimental effect on all aspects of the patient's quality of life; the majority of which is driven by headache [Kleinschmidt, 2000, Mulla, 2015; Daniels, 2007; Digre 2015]. IIH also impacts visual function with PMD correlating with quality of life [Bruce 2016]. Patient reported outcomes in clinical trials are essential not only to permit health technology assessments and cost effectiveness analysis, but also as key outcomes for a therapy's effectiveness [Deiner, 2019]. There is currently no IIH disease specific quality of life outcome measure.

Whilst there are differences in the choice of the tools used in the trials, they all commonly used the short-form 36 health survey (SF-36) [Mollan, 2021, Wall, 2014, Digre, 2015; Bruce, 2016; Ball, 2011]. The physical component score of the SF-36 has been shown to correlate significantly with changes in ICP [Grech 2021]. The EuroQol –5 dimension (EQ-5D-5L) [Euroqol, 1990] is typically employed for health technology assessments and cost effectiveness [Ottridge, 2017; Ball, 2011]. Using the EQ-5D-5L in isolation may lack sensitivity as compared to the SF-36 for IIH. The National Eye Institute Visual Function Questionnaire-25 and 10-item supplement [Mangione, 2001] has also been utilised to assess visual related quality of life in IIH and is associated with improvement in visual field [Bruce 2016; Mangione 1998; Raphael 2006]. The 10-Item neuro-ophthalmic supplement was found to be significantly discriminating in a previous IIH drug trial [Wall 2014].

1.1.1. Name and Description of the Investigational Product

Patients will receive active treatment, Presendin, or matching placebo.

Presendin is a modified release formulation of exenatide. Exenatide is a GLP-1 receptor agonist currently used in the management of type 2 diabetes. Presendin consists of a drug

part (white or greyish white powder in a clear vial) and a diluent part (colourless liquid in a pre-filled syringe). The drug part is suspended in the diluent part solution and administered as a suspension. The patient or responsible person will be responsible for rehydrating the product for injection. Presendin is administered as a once weekly SC sustained-release injection containing 2.0 mg exenatide. Matching placebo will also be supplied as 2 parts, as visually identical vial and pre-filled syringe. The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. Placebo is administered once weekly as a SC injection.

1.1.2. Non-clinical Studies

Exenatide, the active ingredient of Presendin, has been previously developed and licensed as Byetta for the treatment of type 2 diabetes. A wealth of historical toxicological and pharmacological safety data is available in the public domain. Please see the Investigator's brochure for data from rat and mouse studies which have investigated the Presendin formulation of exenatide.

In vitro and *in vivo* data suggests that the choroid plexus, the CSF secreting structure in the brain, contains GLP-1 receptors [Ast 2020]. Preclinical studies in rodents demonstrate that GLP-1 agonists can regulate cerebrospinal fluid dynamics and reduce ICP [Botfield, 2017].

Nonclinical pharmacology studies have shown that exenatide and GLP-1 agonists bind to and stimulate GLP-1 receptors equipotently. Due to the ability of exenatide to affect fluid homeostasis in the kidney, it was investigated for its potential to modulate CSF secretion and reduce ICP in rats. A single SC injection of exenatide rapidly (within 30 minutes) reduced ICP and maintained lower ICP for 6 days of dosing, suggesting that GLP-1 receptor agonists could provide an alternative treatment for conditions with raised ICP [Botfield, 2017].

Exenatide was subjected to full toxicological assessments during its nonclinical development programme, details of which are publicly available in the Byetta® Product Monograph, 2019 and the FDA Pharmacology Review, June 2004 (Section 15). In summary, no lethality or serious toxicity was observed in mice, rats and monkeys following single doses up to 1500 µg/kg, 3000 µg/kg and 5000 µg/kg respectively. In repeat-dose toxicity studies decreased body weight gain and food consumption, a known pharmacological effect of exenatide, were observed in all studies. Exenatide caused no mortality or target organ toxicities in mice, rats and monkeys at doses up to 760µg/kg/day (182 days), 250 µg/kg/day (91 days), or 150 µg/kg/day (273 days) respectively. Reproductive toxicity data from animal studies showed that Byetta had a toxicological effect on foetal development at three times the human exposure levels in treatment of

diabetes. A summary of the findings of the exenatide toxicological assessment programme is presented in the Investigator Brochure for Presendin.

1.1.3. Clinical Studies

Exenatide has undergone extensive healthy volunteer studies and clinical trials for over 15 years. It is licensed as a formulation for SC injection to be used in conjunction with diet and exercise to improve glycaemic control in adults with type 2 diabetes. Details of the trials conducted on exenatide, SC injection formulation, are presented in the Byetta Product Monograph (Section 15). Data from these studies are notable as the dose of exenatide to be used in the indication of IIH is intended to produce exposure levels not exceeding those experienced by patients receiving Byetta. It is anticipated that the proposed therapeutic dose of exenatide, in the modified release formulation Presendin, for treatment of IIH will be within the approved dose range of Byetta, achieving a level of total systemic exposure comparable with the immediate release Byetta formulation. Therefore, safety data available from the Byetta clinical development program are considered relevant and supportive of exenatide development in IIH.

The efficacy of exenatide (Byetta) was evaluated in a Phase 2 randomised, placebo controlled, double-blind trial of exenatide in patients with active IIH (IIH:Pressure Trial). Sixteen patients with a diagnosis of active IIH (LP opening pressure >25 cm CSF and papilloedema) were identified and recruited to the trial. Participants had a telemetric ICP monitor implanted and were randomised to either exenatide (first dose was 2. 0 mcg followed by 10 mcg BD sub-cutaneous) or a matched placebo; allocation was 1:1. The treatment duration was 12 weeks. The trial was powered to seek significance to at least alpha < 0.1 and power at least 80% using equal group sizes. Data was analysed by hierarchical regression analysis. 16 participants were recruited, 15 were randomised and completed the study. At baseline the mean age was 28 ± 9 years, BMI 38.1 ± 6.2 kg/m2, ICP 23.5 ± 3.9 (equivalent to 32.0 ± 5.3 cm CSF). The primary outcome, change in intracranial pressure between arms, was significant: at 2.5 hours -4.2 ± 2.1 mmHg (equivalent to 5.7 ± 2.9 cm CSF), p=0.04, at 24 hours -4.7 ± 2.1 mmHg (equivalent to 6.4 ± 2.9 cm CSF), p=0.03, and at 12 weeks -4.1 ± 2.2 mmHg (equivalent to 5.6 ± 3.0 cm CSF), p=0.05. A significant reduction in monthly headache days was also observed amongst those on exenatide (-7.7 ± 9.2, p-0.069). LogMar visual acuity also significantly improved in the exenatide treated arm (-0.1 ± 0.05, p=0.036). No significant weight loss was observed in either arm and hence weight change is unlikely to have contributed to the reduction kin ICP observed. Exenatide was safe and well tolerated: no treatment related SAE's were reported, 8 adverse events were reported in those taking exenatide. The most frequent adverse event, amongst those taking exenatide, was nausea (7 reports), the majority of these were mild and all reports were self-limiting. There were no patient withdrawals due to adverse events.

1.1.4. Trial Conduct

This trial will be conducted in accordance with the requirements of this document (the Clinical Trial Protocol), the Trial Reference Manual and also in accordance with the following as per country specific requirements:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)
- The United Kingdom Statutory Instrument 2004 No. 1031 and UKSI 2006 No.1928
- European Union Directives 2001/20/EC and 2005/28/EC
- United States Code of Federal Regulations Title 21
- The Australian Therapeutic Goods Act, 1989, amended December 2020 and Therapeutic Goods Regulations, 1990, amended January 2021
- Other country specific laws and regulations
- Any amendments to these regulations

1.2. Risk/Benefit Assessment

Current treatments for IIH have limited efficacy and can cause disabling side effects. Acetazolamide, the most commonly used drug (off licence) has a high side effect profile (48% discontinued in a clinical trial due to intolerable side effects) [Ball, 2011]. Although IIH is a rare condition, incidence is rising with rising obesity trends. Improving IIH morbidity with new therapeutics is clearly an unmet need.

Safety data for Presendin (exenatide) is based on the IB (Peptron Inc.). Warnings include pancreatitis, hypoglycaemia when used in combination with a sulfonylurea, renal impairment, severe gastrointestinal disease and hypersensitivity.

Invex Therapeutics has considered these warnings and has defined eligibility criteria to ensure patient safety is paramount. As such patients with known contraindications to GLP-1 agonists, such as pancreatitis, ketoacidosis, severe gastrointestinal disease and renal impairment, will not be included. Additionally, diabetic patients receiving glucose lowering medication will be excluded.

An Independent Adjudication Committee (IAC), as described in Section 14.5, will assist the Investigators (when required) with the eligibility criteria of the patients to be enrolled,

and also to determine treatment failures to ensure patient safety and the efficacy of the trial.

The most common adverse reactions experienced with exenatide are nausea, hypoglycaemia (only when used with other glucose lowering drugs, but these patients are excluded from the trial), vomiting, diarrhoea, feeling jittery, dizziness, headache and dyspepsia.

Patients receiving the active treatment during the randomised period may benefit by experiencing an improvement in their IIH symptoms, although this cannot be guaranteed.

2. OBJECTIVES

2.1. Primary Objective

To determine the efficacy of Presendin administered subcutaneously once weekly for 24 weeks to patients with IIH, as determined by change in ICP, as measured by LP at baseline and at 24 weeks.

The baseline LP is the diagnostic LP.

2.2. Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation as measured by Humphrey Visual Field analysis (24-2 SITA-Standard)
- Papilloedema by change in optical coherence tomography (retinal nerve fibre layer (RNFL) thickness and optic nerve head size)
- Monthly headache days (MHD)
- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

2.3. Safety Objective

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

2.4. Exploratory Objectives

To determine the effect of Presendin on:

- Macular ganglion cell layer/complex thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes
- Body Mass Index
- Body Weight
- Health Utilisation

3. ENDPOINTS

3.1. Primary Endpoint

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

The baseline LP is the diagnostic LP.

3.2. Secondary Endpoints

- Perimetric Mean Deviation
- Retinal nerve fibre layer (RNFL) thickness
- Optic nerve head size
- The number of monthly headache days (MHD). Monthly headache days will include all headache days, defined as those with an onset, continuation or recurrence, any severity or phenotype of headache, lasting at least 30 minutes or which require acute headache analgesia.

- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

3.3. Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), , serious adverse events (SAEs)
- Resting 12-lead electrocardiogram
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

3.4. Exploratory Endpoints

- Macular ganglion cell layer/complex thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes (PRO):
  - Visual Function Questionnaire-25 and 10-item supplement
  - Headache Impact Test-6
  - 36-item short form survey

- EuroQol -5 dimension -5 level survey
- Patient Global Impression of Change

- Body Mass Index
- Body Weight
- Health Utilisation

4. TRIAL DESIGN

4.1. Summary of Trial Design

4.1.1. Trial Design

This will be a randomised, placebo-controlled, double-blind, multi-centre clinical trial in approximately 240 randomised patients with IIH.

The trial will begin with a 1-week screening period. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period. Headache diaries designed to measure headache frequency have been successfully utilised over shorter time periods in previous IIH trials and noted to be representative [NORDIC, 2018; Mollan, 2021b]. Hence the baseline headache frequency will be calculated over 1 week. Patients will be provided with training on the self-administration of the trial medication from the site trial coordinator and provided with a leaflet to take home at the screening visit. Patients will be asked to self-administer placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed screen failures, and not be randomised into the trial. The purpose of the screening period will be to establish baseline measurements and assess trial eligibility.

The screening period will be followed by a 24-week randomised double-blind treatment period in which patients will be randomised (1:1) to receive a SC dose of either Presendin (containing 2mg of exenatide (active group) or matching placebo (placebo group), self-administered once weekly.

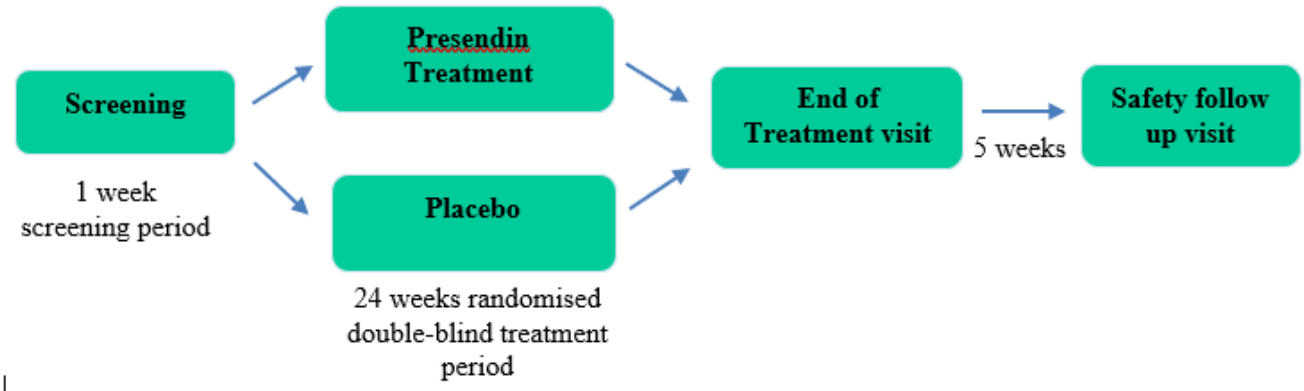
At the end of the randomised treatment period (week 24), all patients will have an end of treatment clinic visit. Five weeks after the end of that treatment visit, an end of trial safety follow-up telephone visit will be performed. In the event of any abnormal safety assessments or ongoing adverse event(s) identified at end of treatment; for example, an abnormal ECG or abnormal routine laboratory results, this visit may be performed at the clinic and a safety follow-up performed as appropriate.

The duration of the randomised treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy by 3 months. Additionally, an alternative off label drug used in IIH (acetazolamide) was evaluated over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk.

Assessments will be performed as outlined in Table 1.

A schematic diagram of the trial can be seen in Figure 1.

Figure 1: Schematic Diagram



4.1.2. Randomisation and Blinding

At the end of the Screening period, eligible patients will be randomised to receive either Presendin or matching placebo in a 1:1 ratio using a computer system to generate randomisation codes.

Investigators and other site personnel, patients, contract research organisation and Sponsor personnel will be blinded regarding the treatment during the randomised period. Only designated unblinded staff, not involved in the operational conduct of the trial, will be aware of the randomisation codes.

The placebo will have the same appearance and reveal no differences, during administration, to either the Investigator or the patient.

4.1.3. Duration of Patient Participation

The duration of the trial for each patient will be up to 30 weeks, which includes a 1-week screening period, a 24-week randomised treatment period and a treatment follow-up period of 5 weeks.

4.2. Stopping Rules

4.2.1. Trial Stopping Rules

There are no trial-specific stopping rules. The Sponsor maintains the right to stop the trial at any point. If this is done, then the Sponsor will provide the Investigators with the rationale for such early termination.

4.2.2. Individual Stopping Rules

Patients will be withdrawn from the trial medication if they are unable to tolerate the trial medication and will continue to attend trial visits as per protocol. See Section 11 for further details. A Data Safety Monitoring Committee (DSMC) will be involved in decisions for patient safety (Section 14.6).

4.3. End of Trial

The end of trial is defined as last patient last visit.

5. TRIAL POPULATION

5.1. Number of Patients

It is anticipated that approximately 350 patients will be required to enter the screening phase for 240 patients to be randomised into the treatment phase.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of new IIH by consensus criteria (see Section 16.1, Appendix 1), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Newly diagnosed patients with screening commenced no more than 4 weeks after the diagnostic LP
4. Lumbar puncture opening pressure ≥ 25 cm cerebrospinal fluid (CSF) at diagnosis
5. Presence of bilateral papilloedema (Frisén grade ≥1). Verification of papilloedema by the OCT Reading Centre. Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerves should be conducted for evaluation by the Independent Adjudication Committee (IAC)
6. Perimetric Mean Deviation (PMD) defined as between -2 to -7 decibels (dB) in at least one eye. Eyes meeting this criteria will be defined as ‘study eyes’

7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses, (reliability confirmed by the Visual Field Reading Centre) in study eyes
8. Two or more headache days over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period
9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.7, Appendix 7 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Able to provide written informed consent

5.2.2. Exclusion Criteria

Patients will not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusion criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth or seventh nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate (including if used as a migraine preventative),

diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)

6. 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

Vision related exclusion criteria:

7. Any disease other than refractive error that causes visual loss in the study eyes. Where there is uncertainly this would be determined by the Independent Adjudication Committee [IAC]
8. Refractive error worse than +/- 6.00 sphere or worse than +/- 3.00 cylinder in study eyes. In addition, participants with myopia of worse than -6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in the study eyes. Where there is uncertainly this would be evaluated by the Independent Adjudication Committee [IAC]

Headache related exclusion criteria:

10. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

11. Untreated previously diagnosed obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
12. Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
13. COVID-19 vaccine within 2 weeks prior to screening
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which may affect the safety of the patient
16. Using any glucose-lowering medication
17. Currently taking warfarin

18. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)
19. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
20. Any of the following abnormalities in clinical laboratory tests at screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
21. Using recreational or illicit drugs at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
22. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period
23. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
24. Any contraindication to lumbar puncture procedure in the opinion of the investigator
25. Has participated in any other interventional trial within 1 month prior to the screening visit.
26. Is pregnant or breastfeeding

Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2

6. TRIAL ASSESSMENTS AND PROCEDURES

6.1. Procedures at Each Visit

Trial procedures and timings are presented in the Time and Events Table, Table 1.

No procedures should be performed prior to obtaining informed consent. All visits (except telephone call visits) should be performed at the clinic. Should a clinic visit not be possible, due to a patient self-isolating, the visit will be conducted at the earliest opportunity and will not constitute a protocol deviation.

6.1.1. Visit 1 Screening

The screening period must be a minimum of 7 days, up to a maximum of 10 days. Visit procedures can be performed in a single visit or over a number of visits during the screening period. Ideally all screening procedures should be performed on the same day.

- Obtain patient's written informed consent
- Eligibility criteria
    - Including confirmation that diagnostic LP occurred within the last 4 weeks with an opening pressure ≥ 25 cm CSF in lateral decubitus position
- Demographics (sex, age and ethnicity)
- Medical and ophthalmic history
- Concomitant mediation history
- Headache history (including family history of migraine (a first degree relative with and migraine) and headache in the 7 days prior to diagnostic LP)
- Headache preventative medication review
- Headache diary dispensed and diary training – to be performed on first day of screening.
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Height, body weight and BMI
- Full physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram

- Visual Assessments to both eyes
    - Frisén grading will be initially assessed by the site and then the presence of papilloedema verified by the OCT Reading Centre. Where there is uncertainty, fundus photos and or ultrasound scan (B scan) of the optic nerve may be conducted for evaluation by the IAC to confirm eligibility.
    - Optical coherence tomography imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard using a size III white stimulus)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay, and where there is uncertainty about eligibility this should be referred to the IAC.
    - Visual Acuity (LogMAR score)
- Laboratory assessments
- Trial medication training. Patients will be asked to self-administer 1 dose of placebo at the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable will be excluded

6.1.2. Visit 2 Baseline

- Review eligibility criteria
- Concomitant medications review
- Headache preventative medication review

- Review headache diary (Patient must meet required number of headache days as per inclusion criteria. If the headache diary exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit)
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse events review
- Targeted physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Visual Assessments to both eyes
    - Frisén grading will be assessed by the site
    - Optical coherence tomography imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
    - Visual Acuity (LogMAR score)
- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Laboratory assessments

- Anti-Drug Antibodies (ADA) blood sampling
- Patient randomised
- Trial medication training
- Trial medication dispensed and first dose self-administered at clinic. Patients will then be instructed to administer subsequent doses once weekly.
- Pharmacokinetic sampling (post-dose)

6.1.3. Visit 3 Telephone call

All patients will receive a telephone call at visit 3 to conduct headache preventative medication review, check for any AEs or changes in medication, procedures outside of protocol, health utilisation, to remind them to complete their diary and to answer any questions they may have on administration or storage of the trial medication.

6.1.4. Visits 4, 5, 6, 7, 8 and 9 Clinic visits

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI (not visit 4)
- Adverse event review
- Targeted physical examination (visit 6, 8 and 9 only)
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload processes to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.

- Humphrey Visual Field (24-2 SITA-Standard)
    - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
- Visual Acuity (LogMAR score)

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary (not visit 4)
- Health Utilisation Form
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-Drug Antibodies blood sampling
- Trial medication dispensing (not Visit 4) and accountability - patients should be reminded by the trial site to self-administer the trial medication weekly and to return used and unused trial medication at clinic visits

6.1.5. Visit 10

In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.

Where more than one dose has been missed during the 4 weeks preceding visit 10, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days.

- Concomitant medication review
- Headache preventative medication review
- Headache diary review

- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse event review
- Targeted physical examination
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
        - Sites should initially check the scan quality. The OCT scan should then go through the upload process to the OCT Reading Centre, without delay. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.
    - Humphrey Visual Field (24-2 SITA-Standard)
        - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. The report from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
    - Visual Acuity (LogMAR score)
- Lumbar puncture (within 7 days of last dose of trial medication)
    - Lumbar puncture to be performed ideally after visual assessments
    - Performed in the lateral decubitus position according to LP SOP
    - In some cases the lumbar puncture might be conducted using imaging guidance according to the preference of the individual and site. This could be using x-rays, computer tomography or ultrasound guidance.

- If the procedure is not successfully performed it should be re-booked and repeated as soon as possible and the patient should remain on trial medication with the last dose within 7 days of the LP.

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Patient global impression of change question
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-drug antibodies blood sampling
- Trial medication accountability

Where it is not feasible to conduct all of visit 10 procedures on the same day, these could be split provided visual assessments are performed before the LP and the patient remains on trial medication with the last dose within 7 days of the LP.

6.1.6. Visit 11 Follow-Up

This visit will be performed as a telephone call to conduct headache preventative medication review and check for any AEs or changes in medication. In the event of any abnormal safety assessments identified at the end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments.

A urine pregnancy test (for women of childbearing potential) will be performed, this can be conducted at home if the visit is performed by telephone call.

6.1.7. Unscheduled visit for repeat visual assessments

Optional unscheduled visit for visual testing (HVF, OCT, LogMAR) for patients where there is concern about their visual decline or who perform inadequately or where there is technical failure (more than 15% false positive responses or inadequate performance indicated by the Visual Field Reading Centre for HVF; or OCT imaging not of satisfactory quality as determined by the OCT Reading Centre). Imaging only in the study eye(s).

- Optical coherence tomography Imaging

- Sites should initially check the scan quality. The OCT scan should go through the upload process to the OCT Reading Centre. The OCT scan will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will be sent to the site. Where the OCT is of insufficient quality it should be repeated as soon as possible at an unscheduled visit. Where the OCT processing is of insufficient quality it should be reprocessed as soon as possible by the site.

- Humphrey Visual Field (24-2 SITA-Standard)
  - Sites should initially check the performance quality of the HVF (to ensure no more than 15% false positives). The HVF should then be uploaded to the Visual Field Reading Centre without delay (an initial quality assessment takes place during the upload procedure). The HVF will then be reviewed by the Visual Field Reading Centre for a full quality assessment. Quality reports from the Visual Field Reading Centre will be received by the site. Where the visual field is of insufficient quality it should be repeated at an unscheduled visit without delay.
- Visual Acuity (LogMAR score)

6.2. Trial Procedures

6.2.1. Screening Procedures

6.2.1.1. Demographics

The Investigator, or designee, should record the patient's sex, ethnicity, age, height, body weight and BMI at screening.

Ethnicity data will be collected in order to monitor any response differences in IIH disease progression/symptoms in different ethnicities.

6.2.1.2. Medical, Headache and Ophthalmic History

The Investigator, or designee, should record any ongoing co-morbidities and significant medical, headache and ophthalmic history along with the year in which such co-morbidities began (where known).

6.2.1.3. Reporting of Prior and Concomitant Medication

Concomitant treatment is any medication or therapeutic intervention being continued by the patient at trial entry and any new medication received during the trial. Prior treatment

includes previous medications, treatments and interventions received in the past but no longer ongoing.

For this trial, only relevant prior concomitant medications within the last 4 months will be recorded. These include:

- Treatment to lower ICP (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed)
- Headache preventative medication (including oral or botulism toxin A or monoclonal antibodies against CGRP or CGRP antagonists, or greater occipital nerve block)
- GLP-1 receptor agonist
- Warfarin
- Glucose lowering medication
- Recreational or illicit drugs

At every visit the Investigator or a qualified designee will ask the patient about relevant concomitant medication.

No new medication should be started during the trial, unless medically necessary. The patient should be advised to consult the Investigator or designee before taking any prescribed or over-the-counter medications. In the case of headache preventative medications or ICP lowering medications please see details in the rescue therapy section. Acute headache analgesics are permitted and should be reported in the diary.

6.2.2. Safety Procedures

6.2.2.1. Physical Examination

A full physical examination will be performed at the screening visit. At a minimum the following will be assessed: ear, nose and throat, cardiovascular system, pulmonary system, skin, abdomen and neurological system. At all other time points a targeted (symptom directed) examination will be performed at the Investigator's discretion.

6.2.2.2. Twelve- Lead Electrocardiogram

Twelve lead ECGs should be performed at the times outlined in the Time and Events table (Table 1) in a standardized manner, i.e., after the patient has rested in the semi-supine position for at least 10 minutes. Measurements will be made using an ECG

machine that automatically calculates the heart rate and measures PR, RR, QRS, and QT intervals.

All ECG traces will be reviewed and signed by the Investigator or designee and any abnormalities will be marked as clinically significant or not clinically significant.

6.2.2.3. Vital Signs

Vital signs, including systolic and diastolic blood pressure and heart rate, will be measured at the time points specified in Table 1.

Patients should rest in a supine position for 10 minutes before the vital signs are assessed. Three recordings will be taken and averaged.

6.2.2.4. Laboratory Assessments

Blood and urine samples will be processed at the site. Routine biochemistry and haematology samples will be evaluated at the trial appointed central laboratory. PK, ADA and CSF samples will be stored at the central laboratory and evaluated at a qualified international laboratory. Details of handling and shipping are described in the Laboratory Manual.

6.2.2.4.1. Haematology

Blood for the assessment of haematology parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Total blood count; consisting of:
  - Red blood cells
  - Haematocrit
  - Mean cell volume
  - Mean cell haemoglobin
  - Mean cell haemoglobin concentration
  - Glycated haemoglobin (HbA1C)
  - Blood glucose (non-fasting)
  - Platelets
  - White blood cells

- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Coagulation (prothrombin time, international normalised ratio, activated partial thromboplastin time, thrombin time, fibrinogen)
- Basophils

6.2.2.4.2. Clinical Chemistry

Blood for the assessment of clinical chemistry parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen
- Creatinine
- Total bilirubin
- Total protein
- Albumin
- Alanine transaminase
- Aspartate aminotransferase
- Alkaline phosphatase

6.2.2.4.3. Urinalysis

Urine samples will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed at each time point:

- Glucose
- Ketones

- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen

6.2.2.4.4. CSF

CSF sample from visit 10 LP will be retained for future potential analysis of disease and drug related biomarkers.

6.2.2.4.5. Pregnancy

At screening blood will be collected to enable a serum pregnancy test to be performed. At visits thereafter, urine will be collected from female patients of childbearing potential at the times outlined in the Time and Events table (Table 1) to enable highly sensitive urine-based pregnancy tests to be performed. Female patients who are identified as being pregnant during the trial will be withdrawn from further treatment but will continue to attend safety follow-up visits.

The Investigator or designee should report any pregnancies in female patients to the Sponsor or designee, using the Pregnancy Report Form, within 24 hours. The contact details for reporting are:

[redacted]

Female patients or partners of patients who become pregnant should be followed until delivery, stillbirth or termination. The outcome of the pregnancy and, if applicable, the health of the baby, should be reported to the Sponsor using the Pregnancy Report Form.

6.2.2.4.6. Pharmacokinetic sampling

Pharmacokinetic sampling is to characterize the pharmacokinetics of exenatide after once weekly subcutaneous administration of Presendin at the times outlined in the Time and Events table (Table 1).

The primary purpose of the pharmacokinetic sampling is to characterize the steady state concentrations of exenatide. All actual sampling times and dosing times will be recorded.

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.4.7. Anti-drug Antibodies sampling

Anti-drug antibodies sampling will be performed in all subjects at the times outlined in the Time and Events table (Table 1).

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.5. Adverse Events

Patients will be asked non-leading questions to assess how they are feeling at each clinic visit. Adverse events will be assessed and reported as outlined in Section 12.

6.3. Efficacy Procedures

6.3.1. Intracranial Pressure

Assessment of ICP will be measured by LP in the lateral decubitus position. The diagnostic LP is performed by the clinical team prior to recruitment and the measurement must be made from the lateral decubitus position. The research LP will be performed according to LP standard operating procedure (SOP). Lumbar puncture will ideally be performed after visual assessments as outlined in the Time and Events table (Table 1).

In some cases the lumbar puncture might be conducted using imaging guidance according to the preference of the individual and site. This could be using x-rays, computer tomography or ultrasound guidance.

Any additional LP procedures, outside of the protocol would constitute a protocol deviation and ideally should be discussed with the Investigator before the procedure is performed.

Non-protocol LPs should be recorded in the Case Report Form.

6.3.2. Visual Assessments

Visual assessments should be performed on both eyes. All visual assessments should be uploaded without delay on the day of the visit to the OCT and Visual Field Reading Centres. In all cases the site is responsible for initial checks of the clinical data in the wider context of the patient's disease, as well as a data quality check.

6.3.2.1. Frisén grade

At Screening (visit 1) Frisén grading (0 – 5) should initially be performed at the site through a dilated pupil. The presence of papilloedema will be verified by the OCT Reading Centre at screening (visit 1) and a report sent to the site. During screening,

where there is uncertainty regarding the presence of papilloedema and / or Frisén grade a fundus photo and or ultrasound scan (B scan) of the optic nerve may be conducted (or may be requested by the OCT Reading Centre) and if uncertainty persists evaluated by the IAC.

At Baseline (visit 2) sites will reconfirm the Frisén grade

6.3.2.2. Optical Coherence Tomography

Imaging may be acquired using Heidelberg Engineering or Cirrus platforms according to the OCT SOP. Key measures are RNFL, optic nerve head size, and macular ganglion cell layer/complex thickness..

- Sites should initially check the clinical interpretation of the OCT scan and scan quality. The OCT should then go through the upload processes to the OCT Reading Centre. The OCT will then be reviewed by the OCT Reading Centre for a full quality assessment. The report from the OCT Reading Centre will then be sent to the site. Where the OCT is of insufficient quality, it should be repeated as soon as possible. Where the OCT has not been processed correctly at the site the processing should be re-performed as soon as possible thereafter. Repeated or reprocessed images would then be again transmitted to the OCT Reading Centre for a full assessment.
- If the site is concerned with the OCT findings, suggesting that the patient is a potential treatment failure and may require rescue therapy, the OCT Reading Centre review will be prioritised and when indicated expedited to the IAC.

6.3.2.3. Humphrey Visual Field

The visual field will be measured by Humphrey Visual Field analysis (24-2 SITA-Standard) including standardised refraction as indicated, according to the Visual Field Centre SOP (Manual of Procedures).

- At screening HVF will be reviewed by the Visual Field Reading Centre to confirm eligibility.
- Inability to perform a reliable visual field examination as deemed by the Visual Field Reading Centre in study eyes (including >15% false positives), is an exclusion criterion. HVF can be repeated to obtain as assessment with reliable performance.
- If the site is concerned with the HVF findings, suggesting that the patient is a treatment failure and may require rescue therapy, the Visual Field Reading Centre review will be prioritised and when indicated expedited to the IAC.

6.3.2.4. Visual Acuity

Assessment of visual acuity will be recorded using a LogMAR chart (unaided, best corrected, and with pin hole).

6.3.3. Headache Assessments

Patients will be provided with an electronic/paper diary at screening to complete during the trial. Information collected will be used to assess the following headache parameters:

- Monthly headache days
- Monthly moderate to severe headache days
- Responder rate
- Monthly acute analgesic use
- Headache severity (11-point NRS)

6.3.3.1. Headache Preventative Medication Review

A review of any headache preventative medications taken by the patient will be undertaken at each clinic visit. If the Investigator alters the headache preventative medication, this will be considered rescue medication (Section 10.1.1) and the IAC consulted. Use of headache preventative medication will be recorded at trial visits as outlined in the Time and Events table (Table 1).

Patients will record their acute headache analgesic use in their trial diary.

6.3.4. Patient Reported Outcomes

6.3.4.1. Visual related

Assessment of visual related quality of life will be derived from self-reported responses to the VFQ-25-10 item supp (see Section 16.5 Appendix 5).

6.3.4.2. Health-related

Assessment of health-related quality of life will be derived from self-reported responses using the following questionnaires:

- 36-item short form survey
- EuroQol -5 dimension -5 level survey

A Healthcare Utilisation Form will be completed by the trial site staff at clinic visits.

All questionnaires can be found in Section 16, Appendix 2 for SF-36 and Appendix 3 for the EuroQoL- 5D-5L survey.

6.3.4.3. Headache related Quality of Life

Assessment of headache-related quality of life will be derived from self-reported responses to the Headache Impact Test-6 questionnaire and performed at time points as outlined in the Time and Events table (Table 1). A copy of this questionnaire can be found in Section 16.4, Appendix 4.

6.3.4.4. Patient Global Impression of Change

The Patient Global Impression of Change will be conducted at visit 10, as outlined in the Time and Events table (Table 1).

It is a single item questionnaire using a seven-point verbal response scale to assess overall change in the patient's status since taking trial medication. A copy of this questionnaire can be found in Section 16.6, Appendix 6

6.3.5. Body Weight and Body Mass Index

The patient's body weight and BMI will be measured at the time points as outlined in the Time and Events table (Table 1).

The patient's height will be measured at Screening (shoes off).

7. SAFETY MEASURES DUE TO A GLOBAL CRISIS

The COVID-19 global pandemic presents numerous challenges to the conduct of ongoing clinical trials. In line with the FDA and European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (EMA, 2021), the following protocol considerations are provided to ensure patients safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain. Other unforeseen global crises may occur during the conduct of the study, similar to the COVID-19 global pandemic, in which case the following protocol considerations may also be applied.

Recognizing the flexibility required to manage the impact of the pandemic (or other global crisis) on this clinical study, additional details will be added to respective study manuals, project plan documents, and communicated to the investigative sites as needed. For any additional questions, the investigator should confer with the sponsor.

Number of Trial Patients

The evolving situation of the pandemic (or other global crisis) may result in a substantial number of patients' early withdrawal from the study, which could affect the data integrity of the study. Because of this risk, the sponsor may decide to recruit additional patients in the study, beyond the expected number, to mitigate such risk.

Study Visits

There are a number of on-site visits that would be required to ensure study validity. If there are local travel restrictions, isolation requirements, or the investigator determines it to be unsafe for patients to attend their scheduled study visits, the site staff may conduct certain visits via telemedicine (phone or video calls) to minimize patient risk as follows.

Screening Period

The following visit must be performed in person:

- Screening/Visit 1
  Note: To minimize direct, in-person contact between site personnel and patients, certain screening procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site.
  Specifically, the following procedures may be done remotely:
  - Informed consent (where applicable, per approved IRB/IEC process)
  - Demography

- Medical and ophthalmic history
- Concomitant medication history
- Headache history
- Headache preventative medication review
- Train and dispense headache diary
- Trial medication training

Randomised period

- Baseline (Visit 2)
  There are essential aspects to the baseline visit which must be performed in person.
  If the baseline visit is delayed the headache diary should utilise the preceding 7 days data. Where the visit is delayed by more than 10 days due to a global crisis the patient will be considered to have failed screening. Patients who screen failed due to the pandemic (or other global crisis) may be rescreened at a later time, if feasible.

  To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:
  - Concomitant medication review
  - Headache preventative medication review
  - Headache diary review
  - Adverse events
  - Patient reported outcomes
  - Health utilisation form

- Visit 4, 5, 6, 7, and 8
  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination

- Urine pregnancy test
- Electrocardiogram
- Optical coherence tomography imaging
- Humphrey Visual Field
- Visual acuity testing
- Laboratory assessments
- Pharmacokinetic sampling
- Anti-drug antibodies sampling

To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Adverse events
- Patient reported outcomes
- Health utilisation form

- Visit 10

  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination
  - Urine pregnancy test
  - Electrocardiogram
  - Optical coherence tomography imaging
  - Humphrey Visual Field
  - Visual acuity testing
  - Laboratory assessments
  - Pharmacokinetic sampling
  - Anti-drug antibodies sampling

- Lumbar puncture*

* Lumbar puncture to be ideally performed after visual assessments. In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days, if possible, but this can be extended according to local government policy if a patient is unable to attend (for example if a patient is self-isolating) as long as medication use is maintained as above.

- Follow up/ Visit 11

  This should be performed as a telephone visit unless clinical contact is necessary, as per protocol. Where face to face contact is required, this should be conducted at the earliest available opportunity.

Study Drug Dispensation and Distribution

If a patient is not able to attend a clinic visit, to ensure the continuity of providing patients' study drug within the constraints imposed by the pandemic (or other global crisis), the site staff may decide to supply study drug to patient as follows:

- Adequate supplies of study drug can be shipped to the patient by the study staff using a third-party service with approval from the patient. The third-party vendor will be agreed upon with the sponsor.
- The patient may request, with prior arrangement/agreement with the site, an authorized individual (a relative or delegate) to retrieve the study drug from the study site if the patient is unable to personally to do so.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (e.g., phone

calls, emails, video visits) with the sites to get information on study progress, patient status, and information on issue resolution as detailed in the Data Monitoring Guidelines, Remote source data verification.

If the trial site monitor cannot be on-site to carry out the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be carried out by a pharmacist from the site pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the site pharmacy directly, or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts with Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of patient for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

Clinic visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as the crisis-related limitations permit.

All safety data that are possible to obtain locally should be collected at a remote visit. These measurements may include the use of local practitioners and resources.

Exceptional measures taken in response to a crisis (e.g., COVID-19) and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3 guidance.

8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

Patients will receive lifestyle advice as per routine care from their treating physician.

9. INVESTIGATIONAL PRODUCT

9.1. Dosage and Administration

9.1.1. Randomised Period

During the 24-week randomised treatment period (Figure 1) patients will be randomised in a 1:1 ratio to receive active treatment or placebo.

Either

Presendin (2.0mg exenatide) as a SC injection, self-administered once weekly.

Presendin is supplied as 2 parts, one vial consisting of a drug part (white or grayish white powder in a clear vial) and one pre-filled syringe containing the diluent part (colourless liquid). The drug part is suspended in the diluent part solution and administered as a suspension.

or

Placebo as a SC injection, self-administered once weekly.

Placebo is supplied as 2 parts (visually identical to the Presendin vial and pre-filled diluent syringe). The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. The drug part is suspended in the diluent part solution and administered as a suspension.

9.2. Dose Rationale

The proposed 2mg weekly dose was based on the pharmacokinetic performance of the Peptron formulation (PT320). Pharmacokinetic profiles obtained after repeated once weekly dosing of 2mg of PT320 s.c. (as specified in the Presendin IB phase 2 clinical study in patients with type 2 diabetes) were comparable to those predicted by the population PK model developed for weekly s.c. administration of the recommended dose of the 2mg Bydureon extended-release formulation [Cirincione 2017],with time to reach the steady state slightly shorter for PT320 than for Bydureon (7-8 weeks vs 8-10 weeks) and with steady state plasma concentrations remaining within a comparable range for both products. Based on the same molecule and dose, comparable plasma concentrations for PT320 and Bydureon and the established safety profile of Bydureon a similarly acceptable safety and tolerability profile for PT320 is expected.

9.3. Maintaining the Blind

This is a double-blind trial.

A computer/website system will be used to maintain the blind for this trial. The site will be provided with website login details for the system. If the Investigator needs to unblind a patient's treatment, due to a medical emergency, the website should be accessed to unblind for that patient. .

The responsibility to break the treatment code in emergency situations resides solely with the investigator.

9.4. Treatment Assignment

Patients will be randomised in a ratio of 1:1 to receive active treatment (Presendin) or placebo. A computer/website system will be used to randomly assign each patient to a treatment arm.

9.5. Packaging and Labelling

Individual supplies of trial medication will be provided to the sites in a double-blind format. The labels will contain all information required to meet the applicable local regulatory requirements.

Further information on packaging, labelling and dispensing are included in the Pharmacy Manual.

9.6. Preparation

Each dose of trial medication is provided as two parts, a single use vial and a pre-filled syringe of diluent. Patients will receive training and be provided with an instruction sheet with details, on how to store, prepare, self-administer and discard/keep used trial medication.

9.7. Handling and Storage

Presendin, the active trial medication, contains the active ingredient, exenatide, which is hygroscopic and light sensitive and must be protected from light during storage. Prior to use, all trial medication should be stored refrigerated at 2-8ºC.

9.8. Product Accountability and Assessment of Compliance

In accordance with International Council of Harmonisation – Good Clinical Practice (ICH-GCP), each trial centre will account for all supplies of trial medication. Details of receipt, storage, assembly, and return will be recorded. The unit of accountability will be one single active or placebo vial. Needles will be disposed of in a sharps box.

All unused supplies will either be destroyed or returned to the trial Sponsor at the end of the trial in accordance with instruction by the Sponsor.

All trial medication will be self-administered by the patients. If a dose is not administered as planned, patients will record the missed dose in their electronic/paper diaries and it will be documented in the electronic case report form (eCRF).

9.9. Treatment of Investigational Product Overdose

Definition of Overdose: More than 1 (one) dose in 24 hours.

In the event a patient overdoses on trial medication the Investigator should be notified as soon as possible. If symptoms appear, the Investigator will treat the patient according to their clinical judgement depending on the type of clinical signs and symptoms exhibited by the patient. The Sponsor should be notified in writing within 24 hours of the Investigator becoming aware.

Effects of overdose that may be seen include severe nausea, severe vomiting and rapidly declining blood glucose concentrations.

9.10. Occupational Safety

There are no known occupational safety risks to staff. The Material Safety Data Sheet will be made available where required by local regulations.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

10.1. Recording Prior and Concomitant Medication

All relevant medication taken within 4 months of screening should be recorded in the eCRF along with all relevant medication taken from the start of the screening period until the final follow-up visit (Section 6.2.1.3).

At a minimum the following information will be collected:

- Generic name
- Dose
- Frequency
- Date started
- If ongoing (or if not, then the date stopped will be recorded)
- Reason for taking the medication

10.1.1. Treatment Failure

Rescue therapy can be initiated when there is a treatment failure. Since perimetric variability increases with increasing visual field damage, a two-tiered approach is used [Wall, 2013].

10.1.1.1. Possible treatment failure

Possible treatment failure is defined as those with baseline PMD between -2 and -3.5dB who experience a decline of > or equal to 2dB. In those with a baseline PMD between -3.5 and -7 dB, those who experience a decline of > or equal to 3 dB.

When a possible treatment failure is identified, perimetry, and if needed, other visual tests, should be repeated at an unscheduled visit.

10.1.1.2. Definite treatment failure

A definite treatment failure occurs when a patient with baseline PMD between -2 and -3.5dB experiences a decline of > or equal to 2dB which remains after repeat perimetry. Or in those with a baseline PMD between -3.5 and -7 dB who experience a decline of > or equal to 3 dB which remains after repeat perimetry.

These cases should be reviewed without delayby the IAC (who will review all visual and clinical data) to confirm or refute a definite treatment failure.

10.1.2. Rescue Therapy/Rescue Intervention for Progressive Visual Loss

When a treatment failure occurs, rescue therapy can be initiated, in addition to study treatment, based on the medical judgement of the Investigator. Decisions should always be discussed with the IAC without delay and if possible before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to be a medical emergency. In all cases the final decision lies with the Investigator.

Patients showing progressive visual loss will be considered for rescue therapy with acetazolamide or an alternative diuretic. In cases where the visual loss is severe and “rapid”, and believed by the Investigator to necessitate surgical intervention, the intervention will be conducted in accordance with local emergency practice.

10.1.2.1. Rescue Therapy for Headache

If the Investigator wishes to alter the headache preventative medication (any drug can be considered), this decision should always be discussed with the IAC before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to

be a medical emergency. Use of headache preventative medication will be recorded at trial visits.

Use of acute headache analgesics is not considered as rescue medication and is permitted but must be documented in the headache diary (monthly analgesic use).

10.2. Prohibited Medications

10.2.1. Prior to screening and randomisation

- Treatment to lower ICP within 1 week prior to screening (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed).
- Exposure to fluoroquinolones, lithium, vitamin A, or tetracyclines within 2 months of diagnostic LP
- Glucagon like peptide-1 receptor agonist within last 4 weeks prior to screening
- Warfarin
- Glucose-lowering medicationCOVID-19 vaccine within 2 weeks prior to screening
- Recreational or illicit drugs during screening period

  Note: Use of headache preventative medication is allowed at enrolment (except for Topiramate). Changes to headache preventative medication during the trial should be made in consultation with the IAC – see section 10.1.2.

10.2.2. During the trial

- Treatment to lower ICP (e.g., acetazolamide, topiramate (including if used as a migraine preventative), diuretics, glucocorticoids (I.V., injectable steroids or oral (including dexamethasone and prednisolone)). (Nasal, inhaled, or topical steroids are allowed). These will all be considered rescue medication (Section 10.1.2) and the IAC consulted. Use will be considered a protocol deviation.
- If the Investigator alters the headache preventative medication (including oral or botulism toxin A or monoclonal antibodies against CGRP or CGRP antagonists, or greater occipital nerve block) this will be considered headache rescue medication (Section 10.1.2) and the IAC consulted.
- Glucagon like peptide-1 receptor agonists
- Recreational or illicit drugs
- Warfarin
- Glucose-lowering medication
- Regarding COVID-19 vaccination, the risks of receiving or not receiving the vaccination have been considered in relation to the IMP and no additional risks are envisaged. Hence patients may choose to have or not have COVID-19 vaccination or booster during this trial.

The investigator should follow the cautions and guidance on the management of other concomitant medication or DDIs as detailed in section 9.2.5.2 (Drug-Drug Interactions) of the IB.

11. PATIENT COMPLETION AND WITHDRAWAL

11.1. Patient Completion

Patients will be classed as having completed the trial once they have completed all required trial visits. See Section 11.2.1 for early discontinuations.

11.2. Patient Withdrawal

11.2.1. Patient Withdrawal from Trial Treatment

A patient will be withdrawn from treatment for any of the following reasons:

- Withdrawal of consent to continue in the trial. The reason for this will be documented if provided
- The Investigator or Sponsor, for any reason, decides the patient should be withdrawn from the treatment
- Lack of compliance with the trial medication is classified as <75% or >125% of scheduled doses over the course of the trial, excluding supply issues
- Adverse events, which cannot be tolerated by the patient
- Pregnancy during the treatment period

Patients will be encouraged to continue in the trial to the end of the randomised treatment period even if they stop trial medication so that data can be collected for the Intention-To-Treat (ITT) population.

If a patient is withdrawn from treatment during the randomised treatment period, they will be encouraged to return for all trial visits up to visit 10. If a patient does not want to return then at a minimum they should be encouraged to attend for visit 11 procedures as a safety follow-up visit.

11.3. Treatment after the End of the Trial

Patients will not be provided with trial medication following the end of the trial.

11.4. Screen and Baseline Failures

Information will be collected on all patients who sign the Informed Consent Form (ICF).

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

12.1.1. Causal Relationship

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration

along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

- Probable relationship: event occurs in a plausible time relationship to the medication administration and cannot be explained by concurrent disease or other drugs or chemicals; the response to the withdrawal of the drug should be clinically plausible
- Possible relationship: event occurs with a reasonable time sequence to the medication administration, but could also be explained by concurrent disease or other drugs or chemicals; information on the drug withdrawal may be lacking or unclear
- Unlikely relationship: event occurs with little temporal relationship to the medication administration and other factors such as drugs, chemicals or underlying disease provide plausible explanations
- Not related: event has no temporal relationship to the medication administration or there is a definite alternative aetiology

12.1.2. Severity Criteria

An assessment of severity grade will be made using the following categorical descriptors:

- Grade 1 means a relatively minor side effect
- Grade 2 means a moderate side-effect
- Grade 3 means a severe or medically significant but not immediately life-threatening side-effect
- Grade 4 means life-threatening consequences
- Grade 5 death related to AE

The exact definition of each number in the scale depends on the particular side effect according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [CTCAE].

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g., laboratory abnormalities).

Adverse events occurring as a result of LP should be specifically recorded. Occurrence of post lumbar headache will be specifically reported.

12.1.3. Reporting Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of

the patient's final safety follow-up visit. The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol. Adverse events reported after dosing will be classed as treatment emergent AEs.

All AEs, regardless of seriousness, severity, or presumed relationship to trial therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the source documents and the eCRF their opinion concerning the relationship of the AE to trial therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

The patient must be provided, on the first day of trial medication (Day 1), with a "patient card" indicating the following:

- Patient number
- Name of the investigational product
- Investigator's name and 24-hour contact information
- Statement that the patient is participating in a clinical trial

12.2. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Deterioration of IIH necessitating CSF shunting or optic nerve sheath fenestration or dural venous sinus stenting will be recorded as an SAE and reported.

Deterioration of IIH necessitating hospital admission will be recorded as an SAE and reported.

Pre-defined exclusions:

- Hospitalisation for unrelated elective procedures
- Post LP headache

12.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to the trial medication and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator Brochure) and serious.

12.2.2. Expected Adverse Events

Perceived deterioration of IIH necessitating attendance or admission to hospital will not be reported as an SAE, but these events will be reported and recorded at follow-up. Non-protocol LPs will be reported at follow-up.

12.2.3. Reporting Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor designee (contract research organisation) within 24 hours of their knowledge of the event.

SAEs will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's final safety follow-up visit.

Information regarding SAEs will be transmitted to the Sponsor’s safety contact using the SAE Form, which must be completed and signed by the Investigator, and transmitted to the Sponsor’s safety contact within 24 hours.

The contact details are:

[redacted]

The Sponsor assumes responsibility for appropriate reporting of SAEs or SUSARs to the regulatory authorities. The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee (IEC) that approved the protocol unless otherwise required and documented by the IEC.

An annual safety report will be submitted to the Institutional Review Board once a year via the Investigator.

12.3. Reporting and Handling of Pregnancies

Pregnant patients will be withdrawn from the trial.

Female patients will be instructed to notify the Investigator immediately if they become pregnant during the trial and up to 12 weeks after discontinuation/completion of trial medication. Pregnant patients will be withdrawn from further trial treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the trial.

A pregnancy as such is not an AE, unless there is a possibility that the trial medication has interfered with the efficiency of any contraceptive measures. The Investigator should report all pregnancies to the Sponsor contact or designee within 24 hours of being informed of them. The pregnancy report form should be used instead of the SAE form.

The pregnant patients will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

Patients will give consent on enrolment that the Investigator will report any pregnancy to the Sponsor and that further information will be collected until delivery.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalised prior to database lock providing detailed methods for the analyses outlined below.

13.1. Hypotheses

This trial compares outcomes in IIH patients under Presendin and matched placebo. The primary hypothesis that will be tested is:

- The ICP measurement in the Presendin group is equal to the ICP measurement in the placebo group at Week 24; against the alternative that the outcomes differ

13.2. Trial Design Considerations

13.2.1. Sample Size Assumptions

The target sample size for the trial is 240 randomised patients, i.e., 120 patients per arm. We justify this figure in the following sections. The two outcomes for which we sought to power the study are ICP and PMD.

13.2.1.1. Intracranial Pressure Power

The most difficult parameters to specify for a sample size calculation pertain to the variability of outcomes. We present a brief summary of the literature. Baseline standard deviations (SD) of ICP in previous trials were: 5.4 (n=10) and 6.3 (n=17) in the Drug Trial [Markey, 2017]; 5.0 (n=16) (data on file); and 5.7 (n=32) and 5.3 (n=30) in the Weight Trial [Ottridge, 2017]. Post-baseline standard deviations were slightly lower (and less than 6.0) in three of these five arms; and increased slightly in one (but remained less than 6.0). The post-baseline standard deviation however increased to over 8.0 in the surgery arm of the Weight Trial because the surgical intervention dramatically impacted ICP in some patients. In the NORDIC trial [Wall, 2014] however, the standard deviation of baseline ICP was much higher, at 9.4 in the treatment arm (n=86). Seeking to avoid underpowering the study, we elected to proceed with the SD estimate for the NORDIC trial as this is the most similar trial population to the planned IIH EVOLVE trial (both recruiting acute IIH). We assume that control arm baseline and 24-week ICP SD equals 9.4, Presendin baseline ICP SD equals 9.4, and Presendin 24-week ICP SD equals 10.4. These values assume the variability of ICP measures in untreated patients is as high as has been seen in the NORDIC trial and assumes that the variability in treated patients is slightly higher still. We anticipate that the standard deviation will be slightly higher in the experimental arm as treatment effects will potentially manifest changes in ICP. However, we do not expect such variability to be as inflated in this trial relative to control as it was

in the Weight Trial because of the likely difference in treatment effect between surgical and drug interventions.

Under this parameterisation, when testing for a difference between arms at 24-weeks of 5 CSF (justified below) using a total sample size of 240, assuming that up to 50% of observations are missing (i.e. 60 final LPs are completed in each arm), using a 5% significance level by Analysis of Covariance (ANCOVA) adjusted for baseline ICP, the two stratification variables, and treatment arm, we expect to have approximately 85% power. If 40% of observations are missing (i.e. 72 final LPs are completed in each arm), we expect power to be 91%. These figures have been inferred by computer simulation. Of the 165 patients in IIHTT [Wall, 2014] it was reported that "only 85 participants (47 [55%] in the [treated] group and 38 [48%] in the placebo group) agreed to a lumbar puncture at month 6."

We expect a high rate of missing data because lumbar puncture is an invasive procedure that patients can find painful and traumatising [Scotton, 2018]. If patients have an unpleasant experience at the diagnostic LP they are also more likely to decline the LP at trial outcome. If patients do decline the final LP, logically it will be because of the baseline experience rather than their prevailing ICP. If data for the LP at 24 weeks is missing, the reason will be recorded.

Outcomes from previous trials show that baseline and post-baseline distributions of ICP show central tendency with approximate symmetry, so we conclude that normality is a reasonable assumption and therefore ANCOVA is a defensible analysis method.

13.2.1.1. Perimetric Mean Deviation Power

We summarise here the estimated power for detecting differences between arms in the PMD outcome measure. In the NORDIC trial [Wall, 2014], the authors observed that the improvement from baseline to 6-months in PMD was 0.71dB greater in the experimental arm than the control arm. Cross-sectional SD of PMD was 1.1-1.2 at baseline. Table 2 in their publication shows that the standard error of mean PMD is higher at 6m than at baseline, likely reflecting a combined effect of missing data at 6-months and greater variability of post-baseline measures. We plan to take repeated measures of PMD at baseline, 2 weeks, 1-month (m), 2m, 3 m, 4m, 5m and 6m. Assuming that the overall SD of PMD scores is 1.8, thus introducing some reasonable inflation on Wall *et al.*'s baseline variability parameter for the reasons identified, using the formula given on p.31 of Diggle, Liang & Zeger (1994) we would expect to require 142 patients in total to detect a difference of 0.71dB (justified below) with 90% power at a 5% significance level, if the serial correlation between repeated measures is 0.4 (and we expect a value in this region) [Diggle, 1994]. If the serial correlation parameter is as low as 0.3, the required sample size increases to 166.

Note that the method used above assumes full follow-up and data collection. Although every effort will be made to collect all outcomes, naturally some missing data is expected. If we inflate the maximum sample size identified above by up to 30% to account for some data loss, we require up to 166 / 0.7 = 237 patients. The assumed 30% missing data rate was adjudged to be realistic by the Sponsor based on previous trials in IIH. Thus, we expect to be able to cover the impact of missing data using the extra patients necessitated by the sample size calculation for ICP.

The above assumes only one eye is measured per patient. In actuality, some patients may provide outcomes for both eyes because any eye that satisfies the eligibility criteria (see Section 5.2) will be enlisted in the study. Put another way, all patients will provide outcomes in at least one eye, and some will provide outcomes in two. Second eyes will naturally be highly correlated with first eyes. From a sample size perspective, this means the additional information in second eyes will be of modest value. Nevertheless, outcomes on second eyes will contain some additional information and should be included in the analysis in the interest of efficiency. When estimating sample size, for the sake of simplicity and because of uncertainty in the rate of eligibility in second eyes, we have assumed that each patient yields outcomes from only one eye. Eligible second eyes will be included in the analysis with appropriate model terms to handle the within-patient correlation (further details are included in the SAP). As such we expect outcomes from second eyes to provide a modest uplift in power to the scenarios presented here.

This section assumes a longitudinal analysis method such as hierarchical regression.

13.2.2. Stratification

At the outset, it is expected that markers of disease severity will be prognostic of potential efficacy. For this reason, it is proposed to stratify randomisation by, baseline ICP (<35cm or ≥35 cm), baseline body mass index (< 30 kg/m^2 or ≥30 kg/m^2) and baseline PMD (worse than or equal to -3.5dB or better than -3.5dB).

13.2.3. Sample Size Sensitivity

13.2.3.1. Clinically Meaningful Effect Sizes

Minimally relevant effect sizes have not been fully determined in IIH given it is a rare disease with relatively few previous trials.

The ICP diagnostic threshold in IIH is 25 cm CSF [Mollan, 2018]. However, it is not necessary to reduce ICP <25 cm CSF to achieve remission from signs and symptoms of IIH in all patients [Sinclair, 2010]. The clinical importance of a particular change in ICP

will vary depending on the starting ICP and the impact this pressure has on vision and headache. Changes in ICP of 5 cm CSF are generally considered meaningful when treating IIH patients. For example, in a clinical study evaluating the benefits of weight loss in IIH patients, a 16.5% (6.2 cm CSF) reduction in ICP resulted in a statistically significant improvement in headache and vision measures as well as quality of life [Sinclair, 2010]. In the IIH Treatment trail (n=165), a study evaluating the drug treatment acetazolamide against placebo, a reduction of -5.9 cm CSF was seen in association with significant improvement in PMD, OCT measures of papilloedema and quality of life measures [Wall, 2014].

The minimally clinically important change in the perimetric mean deviation adopted into clinical practice was stablished by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) group and the IIH Treatment Trial (IIHTT). The investigators found a 0.71dB difference in the PMD between the two trial arms (comparing acetazolamide with placebo) that was clinically meaningful. The change of 0.71dB was interpreted as clinically meaningful as this was accompanied by significant changes in LP opening pressure, papilloedema (measured by OCT), general quality of life and visual related quality of life [Wall, 2014, Bruce, 2016].

The clinically meaningful effect size for MHD reflects that for a phenotypically similar headache, chronic migraine. Recent randomised trials in patients with chronic migraine [Tepper, 2017; Silberstein, 2017], episodic migraine [Goadsby, 2017], or both [Camporeale, 2018] have shown in post-baseline months 1–3, odds of migraine relative to baseline of 0.5–0.8 with placebo and 0.5–0.3 with experimental drugs. Decreases in MHD relative to baseline grew in time, and placebo responses were stronger in chronic migraine than episodic migraine. In the three placebo-controlled, blinded trials, these equated to odds-ratios of migraine compared with placebo of 0.8–0.6, or absolute differences of 1.5–2.5 MHD [Sinclair, 2010; Tepper 2017; Silberstein, 2017; Goadsby, 2017].

13.2.4. Trial Stopping Criteria

There are no trial-specific stopping rules.

13.3. Data Analysis Considerations

13.3.1. Estimands

We have specified intercurrent events that are material to the measurement of our primary and secondary outcomes, and unbiased estimation of treatment effects attributable to Presendin.

ICP-lowering medication include: acetazolamide, topiramate, diuretics, glucocorticoids (oral dexamethasone and oral prednisolone). Headache-preventative medications include: amitriptyline, topiramate, nortriptyline, beta blockers, candesartan, sodium valproate, pizotifen, botox, CGRP-therapy.

13.3.1.1. Outcome: Intracranial pressure (ICP)

13.3.1.1.1. Intercurrent event: ICP-lowering medications

All patients are expected to have elevated ICP because it is a defining characteristic of the disease. ICP is a physiological variable that is unlikely to show spontaneous improvement without treatment. For these reasons, we expect ICP-lowering medication use to be greater in the placebo arm. If a patient takes medication that is intended to reduce their ICP, it is logical to expect that their ICP will be reduced. Outcomes from patients that take ICP-lowering medications will confound the estimation of the causal treatment effect of Presendin. We have no data to estimate the length of effects of ICP-lowering medications. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have used ICP-lowering medications and replace these observations with arm-specific imputations. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin. Patients will consent at enrolment to forgo the use of ICP-lowering medications and be informed that taking ICP-lowering medications during the trial would constitute rescue therapy and a treatment failure and be a protocol deviation.

13.3.1.1.2. Intercurrent event: Off-protocol lumbar punctures

Lumbar punctures are commonly conducted to reduce intracranial pressure [Weisberg, 1977; Johnston, 1981; De Simone, 2005]. In some centres, they are given routinely although this has now been advised against in the International IIH Guidelines (Soler, 1998; Mollan, 2018). As such, they remain a material therapeutic option. LP is expected to reduce ICP mean opening pressure 32 (28-37) cm CSF to 19 (17-21) cm CSF post LP [Yiangou, 2019]. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify change in ICP after an LP, it is expected that effects in the majority of change would have dissipated completely within two months [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have had an off-protocol LP within

two months of the protocol-scheduled 24-week LP and replace these observations with arm-specific imputations. Where patients require off-protocol LP this would be a protocol deviation.

13.3.1.1.3. Inter-current event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in ICP [Sinclair, 2010]., Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure and replace with arm-specific imputations. Patients will be ineligible for the trial if they have had a surgical weight-loss procedure within 3 months of randomisation or fail to confirm that they do not intend to undertake such a procedure during the trial. They will also be informed at enrolment that undergoing a surgical weight-loss procedure would be a protocol deviation.

13.3.1.2. Outcome: Perimetric Mean Deviation (PMD)

13.3.1.2.1. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication (rescue medication due to treatment failure), it is logical to expect that their ICP will decrease and that papilloedema will reduce as a result, allowing visual fields to improve. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the PMD outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.2.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilloedema, allowing visual fields to improve. Patients that have LPs are expected to experience less pressure on the optic nerve, less papilloedema, and have better chances of

their visual fields improving. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilloedema after an LP the consensus of clinicians would predict that effects of the LP on papilloedema and therefore visual fields would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. PMD outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove PMD outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.2.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including improvements in visual fields [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove PMD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.3. Outcome: Papilloedema measured by OCT (optic nerve head size, retinal nerve fibre layer)

13.3.1.3.1. Intercurrent event: ICP-lowering medications

All patients will suffer from papilloedema at enrolment as it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that the papilloedema will reduce in turn. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the OCT outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.3.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the

associated symptoms of the disease, including reducing pressure on the optic nerve and papilloedema. Patients that have LPs are expected to experience less pressure on the optic nerve and therefore relatively less papilloedema. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilloedema after an LP the consensus of clinicians would predict that effects of the LP on papilloedema would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. OCT outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove OCT outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.3.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in papilloedema [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove OCT outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4. Outcome: Monthly headache days (MHD)

13.3.1.4.1. Intercurrent event: Headache-preventative medications

The great majority of patients are expected to suffer from headache because it is a common symptom of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes medication that is intended to prevent headache, it is logical to expect that their headache burden will be decreased. Despite the widely-observed short-term placebo-effect observed in headache outcomes, we expect headache-preventative medication use to be greater in the placebo arm. Outcomes from patients that take headache-preventative medications will confound the estimation of the causal treatment effect of Presendin (more so with botulinum toxin A and CGRP therapies). For these reasons, we propose to remove the headache outcomes following the administration of headache-preventative medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin. Patients who require a change to their headache preventative medications will do this through consultation with the IAC and such a change would be regarded as headache rescue therapy.

13.3.1.4.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing the frequency and intensity of headache. Beneficial effects dissipate with time. Prospective data documents alterations in headache for at least 7 days and whilst there is no prospective longitudinal data over a longer time period consensus amongst clinicians would widely acknowledge that headache in some individuals can be influenced for up to a month [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. MHD outcomes will be recorded daily via diaries. For the reasons stated, we propose to remove MHD outcomes recorded in the 4-weeks following each off-protocol LP and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.3. Intercurrent event: Dramatic weight-loss

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in headache frequency and severity [Sinclair, 2010]. Sudden dramatic weight loss, e.g. arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove MHD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.4. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that headache will reduce as a result. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the MHD outcomes following the administration of ICP-lowering medications and replace these observations with imputations generated by a method suitable for longitudinal data imputation. Outcomes recorded at the unscheduled visit when the treatment failure is confirmed (and just prior to starting ICP lowering medication) will be defined as the last analysed visit. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.5. Primary Estimand (Hypothetical assuming no concurrent procedures, irrespective of adherence to treatment)

The primary estimand is defined as the following for the primary endpoint:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect ICP.

The primary estimand for the initial secondary endpoint will be handled similarly to the primary endpoint using the "Hypothetical" approach. The initial secondary endpoint is defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect PMD.

13.3.1.6. Secondary Estimand (Hypothetical)

The secondary estimand for the primary endpoint is defined as follows:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect ICP.

The secondary estimand for the initial secondary endpoint will be defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect PMD.

All details will be defined in the SAP.

13.3.2. Analysis Populations

The following analysis populations are planned for this trial:

- **Safety Population:** The Safety population includes all patients randomised to treatment who receive at least one dose of trial medication. This will be the population used for all safety analyses unless otherwise specified.
- **Intent-To-Treat Population (ITT):** The ITT population includes all patients randomised to treatment. This will be the main population for all efficacy analyses unless otherwise specified.
- **Per Protocol (PP)**: The PP population includes all patients randomised to treatment without important non-evaluable protocol deviations. Only protocol deviations with the potential to affect the trial results significantly, or to invalidate the interpretation of the data obtained, will lead to exclusion of patients from the PP population. Protocol deviations to be considered will include (but will not be limited to):
    - Failure to meet inclusion/exclusion criteria
    - Wrong treatment or incorrect volume of drug administration
    - Prohibited concomitant medications
    - Compliance of less than 75% or>125% with trial drug administration
    - Use of rescue procedures, including, off-protocol LPs, LP shunts or bariatric surgery

Assignment of patients to populations will be confirmed at a blinded data review meeting to be held before the trial database is locked.

If a patient is randomised incorrectly or is administered the incorrect trial medication, analyses of the ITT will be based on the assigned treatment, whereas all other analyses will be based on the actual treatment received.

13.3.3. Treatment Comparisons

Treatment comparisons will be undertaken between active and control groups. The primary outcome will be analysed as described in Section 13.2.1.

13.3.4. Safety Analyses

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, and ECG results.

All safety analyses will be performed on the Safety population.

13.3.4.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary (the most recent version before starting the trial will be used).

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

The number and percentage of patients reporting TEAEs, grouped by MedDRA system organ class and preferred term will be tabulated by treatment group. Summaries will be presented for all TEAEs, TEAEs by severity and TEAEs by relationship to trial medication.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged. The observation period in which an AE started will also be provided.

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed by trial arm. Treatment failures will be displayed by trial arm.

13.3.4.2. Clinical Laboratory Evaluations

Laboratory test results for each biochemistry and haematology parameter will be summarized descriptively by treatment group and time point as both observed values and change from baseline values.

The number of patients with clinical laboratory (biochemistry, haematology, and urinalysis) values categorized as below, within, or above the normal ranges (or as either normal or abnormal for urinalysis variables that do not have quantitative ranges), will be tabulated in relation to baseline (shift tables), for each clinical laboratory analyte by treatment group and time point.

Laboratory values will be displayed in the data listings and those that are outside the reference ranges will be flagged, along with corresponding normal ranges. Any patients with any markedly abnormal laboratory results will also be provided in a listing.

Pregnancy test results including reason, if not performed, will be listed.

13.3.4.3. Vital Signs and Body Mass Index Evaluations

Descriptive summaries of observed values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure and heart rate by treatment group and time point.

Body mass index will be derived at Screening, Baseline and Weeks 4, 8, 16, 24, 32 and 48 using height captured at Screening and weight at the respective assessment. Body mass index and weight will be summarized descriptively by treatment group and time point as both observed values and change from baseline values for Safety and ITT populations.

13.3.4.4. Electrocardiogram

Descriptive statistics of observed values and change from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected according to Fridericia's formula (QTcF). These summaries will be presented by treatment and time point for the Safety population.

The number and percentage of patients with values beyond clinically important limits will be summarised including those with an increase in QTcF >30 msec increase from baseline and >60 msec increase from baseline or those with an absolute QTcF value of >450 msec (male patients) or >470 msec (female patients).

13.3.4.1. Other Safety Evaluations

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed by trial arm.

13.3.5. Patient Reported Outcomes Analyses

All patient reported outcome endpoints (VFQ-25, HIT-6, SF-36, EQ-5D-5L) will be analysed as observed and presented with change from baseline in a descriptive summary of treatment and visit

The number and percentages of PGIC responses will be tabulated by treatment and visit.

13.3.6. Missing Data

Although every effort will be made to collect responses from all patients at all scheduled time points, there undoubtedly will be some missing data. The SAP describes in detail steps for dealing with missing data using relevant imputation strategies for specific endpoints that adjust for treatment arm, centre, baseline value, and stratification variables.

13.3.7. Reporting Deviations from the Statistical Plan

Any deviations from the planned analyses will be described and justified in the final clinical trial report.

14. TRIAL ADMINISTRATION

14.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Before initiation of a trial site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the trial in accordance with ICH-GCP and applicable country-specific regulatory requirements.

The trial will be conducted in accordance with all applicable regulatory requirements.

The trial will be conducted in accordance with the EU Clinical Trial Regulation 536/2014, ICH-GCP, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- An IEC/Institutional Review Board review and approval of trial protocol and any subsequent amendments and all ICFs or other information given to the patient
- Patient informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each patient before participation in the trial. Written informed consent will be collected following a review of the patient's information leaflet by the potential patient and a discussion between the patient and the Investigator or suitably qualified designee.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this trial. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site(s) by an outside authority before the Inspectors are permitted access to any of the trial records or the trial areas.

14.2. Trial Monitoring

In accordance with applicable regulations, ICH-GCP, the monitoring plan and the Sponsor's and/or delegate procedures, monitors will contact the site before the start of the trial to review with the site staff the protocol, trial requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data

collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The Sponsor and or delegated monitors will perform risk-based monitoring during the conduct of the trial to ensure that:

- The data are authentic, accurate and complete
- The patient's safety and rights are being protected
- The trial is conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP and all applicable regulatory requirements

14.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all relevant documents.

14.2.2. Data Handling and Record Keeping

Following closure of the trial, the Investigator or head of the medical institution (where applicable) must maintain all site trial records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor SOPs and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of

ownership of the records in the event that the Investigator is no longer associated with the site.

14.3. Provision of Trial Results and Information to Investigators and Publications

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical trial report. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete trial results at a mutually agreeable location.

The Sponsor will also provide the Investigator with the full summary of the trial results. The Investigator is encouraged to share the summary results with the trial patients, as appropriate.

If the Sponsor decides to publish the results, then they will provide the Investigator with an opportunity to review the manuscript. If the Investigator wishes to publish anything related to the trial, then they must provide the Sponsor with the draft publication and allow them no less than 14 days to review the document. The Investigator cannot publish without written authorisation from the Sponsor.

14.4. Data Management

For this trial, patient data will be collected using an eCRF and combined with data provided from other sources in a validated data system. Patient's identifiable data (e.g., name, initials, address etc.) will not be collected in the eCRF or transferred to Invex Therapeutics. Clinical data management will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the statistical analysis or the credibility of the Clinical Study Report. Original CRFs will be retained by Invex Therapeutics; the Investigator will also retain a copy.

Management of clinical data will be performed in accordance with the applicable Sponsor standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Affairs and World Health Organisation Drug dictionary.

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)

b. Maintain SOPs for using these systems

c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)

d. Maintain a security system that prevents unauthorised access to the data

e. Maintain a list of the individuals who are authorised to make data changes

f. Maintain adequate backup of the data

g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)

Training on the use of the electronic data collection system will be provided to all relevant trial site staff.

14.5. Independent Adjudication Committee

The IAC will consist of international medical experts in neurology or ophthalmology who are independent of the Sponsor team.

The role of the IAC will be:

- To support the Investigators with opinions on the eligibility of potential patients
- To provide opinions regarding treatment failure and need for rescue medications required during the trial

Further details on the composition, activities and responsibilities of the IAC can be found in the IAC charter.

14.6. Data Safety Monitoring Committee

Details on the composition, activities and responsibilities of the DSMC can be found in the DSMC charter.

14.7. Insurance, Indemnity and Finance

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this trial against future claims by trial patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all trial procedures have been carried out according to this protocol.

The financial aspects of the trial are addressed in a separate agreement.

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16. APPENDICES PROVIDED FOR TRIAL INVEX-CLIN-IIH-301

16.1. Appendix 1: IIH Diagnostic criteria [Mollan, 2018]

A. Papilloedema

B. Normal neurological examination (except sixth cranial nerve palsy)

C. Neuroimaging: normal brain parenchyma (no hydrocephalus, mass, structural lesion or meningeal enhancement). Venous thrombosis excluded in all.

D. Normal CSF constituents (less than or equal to 7 white cells per mm^3 with normal protein and glucose

E. Elevated lumbar puncture pressure ≥ 25cm CSF

16.2. Appendix 2: 36-item short from survey

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

1776 Main Street
Santa Monica, California 90401-3208

16.3. Appendix 3: EuroQol -5 dimension-5 level survey

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

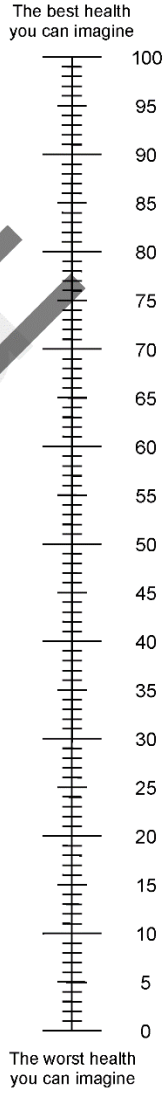
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



16.4. Appendix 4: Headache Impact Test-6

HIT-6™
(VERSION 1.1)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1	When you have headaches, how often is the pain severe?	Never	Rarely	Sometimes	Very Often	Always
2	How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?	Never	Rarely	Sometimes	Very Often	Always
3	When you have a headache, how often do you wish you could lie down?	Never	Rarely	Sometimes	Very Often	Always
4	In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
5	In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
6	In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?	Never	Rarely	Sometimes	Very Often	Always

COLUMN 1 (6 points each)	+	COLUMN 2 (8 points each)	+	COLUMN 3 (10 points each)	+	COLUMN 4 (11 points each)	+	COLUMN 5 (13 points each)

To score, add points for answers in each column.
Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36-78.

HEADACHE IMPACT TEST™

What Does Your Score Mean?

If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your doctor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

About HIT

The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36®* health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

SF-36® is a registered trademark of Medical Outcomes Trust and John E. Ware, Jr.

16.5. Appendix 5: Visual Function Questionnaire-25 & 10-item Supplement

PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

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7/29/96

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don't apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your overall health is:**

(Circle One)

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. **At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

(Circle One)

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Are you currently driving, at least once in a while?

(Circle One)

Yes..... 1 *Skip To Q 15c*

No 2

15a. **IF NO: Have you never driven a car or have you given up driving?**

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. **IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?**

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. **IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have**

(Circle One)

No difficulty at all 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty..... 4

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	*(Circle One On Each Line)* All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0 1 2 3 4 5 6 7 8 9 10

Worst Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0 1 2 3 4 5 6 7 8 9 10

Worst Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognising people you know from across a room?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

10-ITEM NEURO-OPHTHALMIC SUPPLEMENT TO THE NEI-VFQ-25

The following are additional questions and statements about problems that involve your vision or feelings you may have about your vision condition. After each question, there will be a list of possible answers. Please choose the response that best describes your situation.

Please answer all questions as if you were wearing your glasses or contact lenses (if any). Please take as much time as you need to answer each question.

1. How much difficulty do you have performing tasks when your eyes are tired?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

2. Because of your vision, how much difficulty do you have identifying objects or performing tasks in bright sunlight?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

3. Because of your vision, how much difficulty do you have parking a car?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

4. Because of your vision, how much difficulty do you have using a computer?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

For each of the following statements, please indicate if it is definitely true, mostly true, mostly false, or definitely false for you or if you are not sure.

5. I have a feeling that my two eyes see differently, even with correction (glasses or contact lenses).
(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

6. I have a feeling that my eye or eyelid appearance is unusual.

(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

For each of the following, please indicate if it is true for you all, most, some, a little, or none of the time.

7. My vision is blurry, not clear, or "fuzzy."

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

8. I have trouble focusing on or following moving objects.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

9. I have double vision with both eyes open that is not present when either eye is covered.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

10. My eyelid(s) droop.

(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

16.6. Appendix 6: Patient Global Impression of Change

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is

✓*one box only:*

[1] ☐ Very much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very much Worse

16.7. Appendix 7: Contraception

Birth control methods which may be considered as highly effective (that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods).

Patients should be instructed not to take their oral contraceptive within 1 hour prior to administration of trial medication.

Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [1]
- sexual abstinence [2]

[1.] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant.

[2.] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Study Number: INVEX-CLIN-IIH-301 Protocol	Compound No.: Presendin Version: 1.0

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

Effective Date: 02-DEC-2021

Short Title: A Phase III trial to determine the efficacy and safety of Presendin in IIH – IIH EVOLVE

Abstract: Idiopathic intracranial hypertension (IIH) has significant associated morbidity and reduced quality of life. There is a significant risk of visual loss and patients also typically suffer with chronic disabling headaches.

This trial has been designed to evaluate the efficacy and safety of a new release formulation of exenatide (Presendin) in the reduction of intracranial pressure (ICP) in patients with IIH. The primary outcome will be determined by change in ICP, as measured by lumbar puncture (LP).

Eligible, consenting patients will be randomised in a ratio of 1:1 to receive Presendin or placebo as a weekly dose for 24 weeks.

Author	**Department**	**Company**
Emma de Launay	Clinical Operations	Invex Therapeutics Ltd.

Invex Therapeutics
[redacted]

SPONSOR SIGNATURE PAGE

Sponsor Signatory:

A Sinclair — 02.12.2021

Doctor Alexandra Sinclair
MBChB, PhD, FRCP

Chief Scientific Officer

Invex Therapeutics Ltd.

[redacted]

Date

SPONSOR INFORMATION PAGE

Role	Name and Title	Email Address	Address
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Medical Monitor (CRO)	Premier Research Medical Monitor	[redacted]	Premier Research 3800 Paramount Parkway Suite 400 Morrisville NC 27560 USA
Head of Clinical Operations	Carol Parish	[redacted]	Invex Therapeutics Ltd [redacted]
Senior Clinical Trials Manager	Emma de Launay	[redacted]	Invex Therapeutics Ltd [redacted]

Sponsor Contact Information:

Invex Therapeutics Ltd
[redacted]

INVESTIGATOR SIGNATURE PAGE

I, the undersigned, have read and understood the protocol and am aware of my responsibilities as an Investigator. I agree to conduct the study in accordance with this protocol, the Trial Reference Manual and any subsequent amendments, the Declaration of Helsinki, ICH GCP guidelines, and the laws and regulations of the country in which the study is being conducted.

Investigator Name and Qualifications: _____

_____ _____

Investigator Signature Date

[Investigator Affiliation]

INVESTIGATOR INFORMATION PAGE

Details will be provided in the Investigator Site File

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ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
eCRF	Electronic Case Report Form
BMI	Body Mass Index
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
DGM	Data-Generating Models
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
GCL	Ganglion Cell Layer
GLP-1	Glucagon Like Peptide-1
HVF	Humphrey Visual Field
ICF	Informed Consent Form
ICP	Intracranial Pressure
IAC	Independent Adjudication Committee
ICH-GCP	International Council of Harmonisation – Good Clinical Practice
IEC	Independent Ethics Committee
IIH	Idiopathic Intracranial Hypertension
ITT	Intention-to-Treat
LP	Lumbar Puncture
MAR	Missing At Random
MD	Mean Deviation
MHD	Monthly Headache Days
NRS	Numeric Rating Scale
OCT	Optical Coherence Tomography
PK	Pharmacokinetic
PP	Per Protocol
QTcF	QT Interval corrected according to Fridericia's formula
RNFL	Retinal Nerve Fibre Layer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	36-item short form survey
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event

VFQ-25-10 item	Visual Function Questionnaire-25 and 10-item supplement

PROTOCOL SUMMARY

Rationale

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends.

IIH has significant associated morbidity and reduced quality of life. Elevated ICP causes papilloedema universally at disease onset and can lead to permanent visual loss. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Besides risk of visual loss, the most disabling aspect for patients is severe chronic headaches driven by elevated ICP. Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but the high failure rates are high and frequent complications and side effects occur.

A modified release formulation of exenatide (Presendin) has been developed and this trial has been designed to evaluate the efficacy and safety of Presendin in IIH. The modified release formulation has been chosen to enable a once weekly dosing.

Objectives

Primary Objective

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

Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation (PMD) as measured by Humphrey Visual Field analysis (24-2 SITA-Standard)
- Papilloedema by change in optical coherence tomography (optic nerve head volume and retinal nerve fibre layer (RNFL) thickness)
- Monthly headache days (MHD)

- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

Safety Objectives

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

Exploratory Objectives

To determine the effect of Presendin on:

- Ganglion cell layer thickness
- Retinal nerve fibre layer thickness
- Headache responder rate: ≥30% reduction in monthly headache days
- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes (PROs)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Endpoints

Primary Endpoint

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

Secondary Endpoints

- Perimetric Mean Deviation
- Optic nerve head size
- Retinal nerve fibre layer thickness
- The number of monthly headache days (MHD). Monthly headache days will include 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 require acute headache analgesia.
- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

  *criteria defined in rescue therapy section 10.1.1

Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), serious adverse events (SAEs)
- Resting 12-lead ECG
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

Exploratory Endpoints

- Ganglion cell layer thickness

- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes:
  - Visual Function Questionnaire-25 and 10-item supplement (VFQ-25-10 item supp)
  - Headache Impact Test -6 (HIT-6)
  - 36-item short from survey (SF-36)
  - EuroQol -5 dimension -5 level (EQ-5D-5L) survey
  - Patient Global Impression of Change (PGIC)
- Body Mass Index (BMI)
- Body Weight
- Health Utilisation

Trial Design

This is a randomised, placebo-controlled, double-blind, multi-centre trial requiring 240 adult randomised patients with IIH to determine the efficacy and safety of Presendin.

Consenting patients with a diagnosis of IIH will enter a 1-week screening period, in which there will be no investigational treatment, in order to gather baseline measurements and to check eligibility. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period due to the real risk of visual loss. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Mollan, 2021]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

At the screening visit, patients will be provided with training on the self-administration of the trial medication and provided with a leaflet to take home. Patients will be asked to self-administer one (1) dose of placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed a screen failure and will not be randomised into the trial. Eligible patients will then be randomised to receive either Presendin or matching placebo for 24 weeks in a 1:1 ratio. After completion of the randomisation period patients will have an end of treatment clinic visit. Four weeks after the end of treatment visit, an end of trial safety follow up telephone visit will also be performed.

The duration of the double-blind treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy over a 3-month time horizon. Additionally, an alternative off label drug used in IIH (acetazolamide) evaluated efficacy over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk. The duration of the trial for each patient will be up to 30 weeks, which includes a 2-week screening period, a 24-week randomised double-blind treatment period, and a treatment follow-up period of 4 weeks.

Trial Population

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of IIH by consensus criteria (see Section16.1, Appendix 1), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Lumbar puncture opening pressure ≥ 25 cm H_2O cerebrospinal fluid (CSF) at baseline
4. Screening commenced no more than 4 weeks after the diagnostic LP
5. Presence of bilateral papilloedema established from (optical coherence tomography) OCT imaging by the reading centre (Frisén grade ≥1). Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerve should be conducted for evaluation by the reading centre
6. Perimetric mean deviation (PMD) (with mild/moderate visual loss) -2 to -7 decibels (dB)
7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses (reliability confirmed by the reading centre)
8. Greater than 3 days headache over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period
9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.7, Appendix 7 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to

stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])

10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Greater than 2 weeks prior to screening since COVID-19 vaccination (for patients that have received the Covid-19 vaccination)
12. Able to provide written informed consent

Patients must not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusions criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate, diuretics, glucocorticoids (oral dexamethasone and oral prednisolone))

Vision related exclusion criteria:

6. Patients with a past ophthalmic history or diseases causing visual loss, other than cataract extraction, or pre-existing optic disc or retinal diseases that may (in the opinion of the Independent Adjudication Committee [IAC]) affect interpretation of the visual outcomes (e.g., ischaemic optic neuropathy, optic neuritis, pronounced optic disc drusen, optic atrophy, retinal, or choroidal diseases)

7. Existing clinically relevant optic atrophy which, in the opinion of the IAC, may affect interpretation of the visual outcomes
8. Refractive error > +/- 6.00 sphere or > +/- 3.00 cylinder in either eye. In addition, participants with myopia of >-6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Poor Humphrey Visual Field (HVF) test quality which, in the opinion of the IAC, may affect interpretation of the HVF that is not rectified through repeat testing

Headache related exclusion criteria:

10. Has received botulinum toxin or monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or CGRP antagonist injections within the last 4 months for headache or has intention to initiate such injections during the trial
11. Has undergone nerve block (occipital or other) in the head or neck within the last 4 weeks or has intention to undergo nerve block in the head or neck during the trial
12. Does not complete ≥6 days of electronic/paper trial diary during the 7-day screening period

Other exclusion criteria:

13. Untreated documented obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to glucagon like peptide-1 (GLP-1) receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which, in the opinion of the investigator or the IAC, may affect the safety of the patient
16. Currently taking or has received a GLP-1 receptor agonist within the last 4 weeks
17. Using any glucose-lowering medication
18. Currently taking warfarin
19. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is

predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)

20. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
21. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Hemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
22. Using recreational (including cannabidiol) or illicit drugs (including marijuana) at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
23. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period
24. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
25. Has participated in any other interventional trial within 1 month prior to the screening visit. COVID vaccination trials are not considered an exclusion criteria provided the COVID vaccination has occurred > 2 weeks prior to screening visit.
26. Is pregnant or breastfeeding

Trial Assessments

Table 1: Time and Events

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**28**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Informed consent	X											
Inclusion/Exclusion criteria	X	X (review)										
Demography (sex, age, ethnicity)	X											
Medical & Ophthalmic History	X											
Concomitant medication history	X											
Headache history	X											
Concomitant medication review		X	X	X	X	X	X	X	X	X		X
Headache preventative medication review	X	X	X	X	X	X	X	X	X	X		X
Train and dispense headache diary	X											
Review headache diary[1]		X	X	X	X	X	X	X	X	X		
Vital signs[2]	X	X		X	X	X	X	X	X	X		(X)
Height	X											

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**28**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Body weight and BMI	X	X			X	X	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X	X		X
Physical Examination (T = targeted)	X (Full)	X (T)				X (T)		X (T)	X(T)	X (T)		(X)
Urine Pregnancy Test (HCG)[3]	X	X		X	X	X	X	X	X	X		
Electrocardiogram	X	X		X	X	X	X	X	X	X		(X)
OCT Imaging	X	X		X	X	X	X	X	X	X	X	
Assessment of Papilloedema Frisén grade[4]	X	X										
Perimetry	X	X		X	X	X	X	X	X	X	X	
Visual Acuity Testing (LogMAR score)	X	X		X	X	X	X	X	X	X	x	
Patient Reported Outcomes (HIT-6, SF-36, EQ-5D-5L, VFQ-25 & 10-item supp)		X			X	X	X	X	X	X		
Health Utilisation Form		X	X	X	X	X	X	X	X	X		
PGIC assessment										X		
Laboratory assessments[5]	X	X		X	X	X	X	X	X	X		(X)

	SCREENING PERIOD[1]	RANDOMISED PERIOD[11]										FOLLOW UP
Visit	**V1 Clinic**	**V2 Clinic Baseline**	**V3 TC**	**V4 Clinic**	**V5 Clinic**	**V6 Clinic**	**V7 Clinic**	**V8 Clinic**	**V9 Clinic**	**V10[12] Clinic**	**Unscheduled repeat visual assessments[13]**	**V11 TC/Clinic[14]**
Visit Window (days)		**+3**	**± 1**	**± 3**	**± 3**	**± 5**	**± 5**	**± 5**	**± 5**	**± 14**		**± 5**
Month	**0**	**0**			**1**	**2**	**3**	**4**	**5**	**6**		
Week	**-1**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**		**28**
Day	**-7**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Pharmacokinetic (PK) sampling[6]		X[7]		X	X	X	X	X	X	X		
Anti-Drug Antibodies (ADA) sampling		X		X	X	X	X	X	X	X		
Lumbar Puncture[8]										X[9]		
Trial medication training[10]	X	X										
Randomisation		X										
Trial medication Dispensing		X			X	X	X	X	X			
Trial medication Accountability				X	X	X	X	X	X	X		

1 The screening period must be a minimum of 7 days, up to a maximum of 10 days. Patients who do not meet the eligibility criteria based on diary review at randomisation/baseline (e.g., too few headache days or unacceptable concomitant medication use) will be considered screen failures; however, if the patient wishes and the Investigator is in agreement, he/she can be re-screened as a new patient. If the screening period exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e., the 7 days prior to randomisation visit. Trial site research team should review diaries remotely on a weekly basis to ensure compliance and follow up any patients with missing data

2 Vital signs to include: blood pressure and heart rate

3 Women of child-bearing potential

4 Frisén grade will be determined by OCT at a central reading centre at screening to confirm eligibility. Indeterminate cases should be referred to the IAC to allow option to repeat OCT and confirm papilloedema grade prior to randomisation visit

5 Haematology, biochemistry and urinalysis

6 All actual sampling times and dosing times will be recorded

7 Baseline Pre-dose PK blood sample

8 The diagnostic LP will be the baseline LP and must be performed in lateral decubitus position. Patients with ICP <25 cm H_2O CSF at baseline will be excluded

[9] Lumbar puncture to be performed after visual assessment. CSF sample from visit 10 LP will be retained for future potential analysis

[10] Patients will be provided with training on the self-administration of the trial medication. The patient will be asked to self-administer placebo at visit 1 to demonstrate ability to self-inject. Patients who are not comfortable to self-inject will be excluded

[11] If patients discontinue in the double-blind treatment period they will be encouraged to return for all trial visits up to visit 11. If a patient does not want to return for all visits then they will be asked to return at a minimum for visit 11 procedures for safety follow up

[12] In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.
Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days

[13] Optional visit for visual testing (HVF, OCT, LogMar) for patients who perform inadequately or where there is technical failure (more than 15% false positive responses for HVF; or OCT imaging not amenable to segmentation (even when manually corrected) which, in the opinion of the IAC, may affect interpretation of the OCT imaging)

[14] In the event of any abnormal safety assessments identified at end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments

1. INTRODUCTION

1.1. Background and Rational

Idiopathic intracranial hypertension (IIH) is a condition characterised by raised intracranial pressure (ICP) with unknown aetiology, occurring most frequently in obese women of childbearing age. IIH is a rare condition; however, incidence is increasing with rising obesity trends [Mollan, 2019a]. There is a high rate of repeat hospital admission in IIH (increased by 446% in last decade), reflected in escalating healthcare costs (in England £462 million/year predicted by 2030 [Mollan, 2019a] and more than $444 million in the USA [Friesner, 2011]).

The cause of IIH is not fully understood. Recent research has identified that IIH is a disease of systemic metabolic dysregulation characterised by central adiposity [Hornby, 2017], doubled the risk of cardiovascular disease in excess to that mediated by obesity [Adderley, 2019] and adipocyte metabolism primed for weight gain [Westgate, 2021]. Patients are also insulin resistant and have a unique hormone signature of androgen excess in both systemically and in the cerebrospinal fluid.[O'Reilly, 2019]

Morbidity in IIH is due to the elevated intracranial pressure which can cause severe papilloedema (swelling of the optic nerve) which can ultimately lead to blindness. The risk of permanent visual loss is a major concern in IIH. Visual loss occurs in greater than 90% of those with IIH [Wall 1991] and can be severe and permanent in between 5-25%. Headache is an additional major disabler and affects the majority of IIH patients (over 90%) [Yri, 2014; Markey, 2016; Mulla 2015] in the long term. Headaches significantly reducing quality of life [Mulla, 2015; Digre, 2015] are driven by raised intracranial pressure and often have a migraine- like phenotype (> 90%) [Mollan 2021a].

Existing pharmacotherapies are limited. The most frequently used drug therapy, acetazolamide, is used off label and has been shown to have efficacy but due to side effects and treatment failures new drugs are needed. [Piper, 2015; Mollan, 2018; Hoffmann, 2018]. Surgical therapy to lower ICP is a last resort and used as an emergency procedure to save vision but there is a high failure rate and frequent complications. The lack of licenced or targeted treatments in IIH perpetuates poor outcomes for patients. A priority setting exercise was run by patients with IIH (James Lind methodology) [Mollan, 2019c] establishing effective therapy was the top priority from the patient group.

This trial will investigate an alternative therapeutic option for lowering ICP and thereby reducing papilloedema and consequently reducing the risk of visual loss. By reducing ICP it would also aim to improve headache, improving overall patient quality of life in IIH [Mollan 2021a].

Gut neuropeptides are increasingly being recognised for their role in the central nervous system (CNS). A principal gut neuropeptide is glucagon like peptide-1 (GLP-1), which is known to stimulate insulin release, proliferation of pancreatic beta cells and control of glucose regulation in diabetes [Campbell, 2013]. Exenatide is a GLP-1 receptor agonist. It has also been shown to have some actions in the CNS; GLP-1 is involved in regulating satiety and weight through signalling at the hypothalamus [Astrup, 2009]. There is also evidence that GLP-1 may have a role in fluid secretion. In the renal proximal tubule GLP-1 acts to reduce sodium resorption to promote diuresis [Gutzwiller, 2004; Websky, 2014]. The choroid plexus is the fluid secreting structure within the brain producing the majority of CSF. The structure of the choroid plexus epithelial cells is analogous to an inverted renal proximal tubule with a similar mechanism of secretion and hence GLP-1 receptor agonists may also reduce CSF secretion in the brain, leading to a decrease in ICP in patients with IIH.

Exenatide as well as other GLP-1 receptor agonists can lead to weight loss. In diabetic patients weight loss of 2.8 - 4.4 kg has been reported over 6 months [Di Dalmazi 2020; Pujante 2012]. Whilst in non-diabetic overweight and obese patients exenatide caused sufficient weight loss between 2.0 – 5.1 kg [Moreno 2012]. In overweight and obese patients with polycystic ovarian syndrome exenatide led to 2kg more weight loss compared to placebo in over 12 weeks [Liu 2017]. Weight loss with exenatide therapy is increased in the setting of calorie restriction [Rosenstock 2010]. Weight loss is a desirable effect of exenatide as weight loss is therapeutic in IIH. Changes in body weight will be monitored during the trial and the impact on outcomes measures evaluated.

Exenatide (known as Byetta, developed by Amylin Pharmaceuticals LLC) is a currently approved drug for the treatment of type-2 diabetes. It has been identified as a potential candidate for the treatment of neurological conditions involving raised ICP and a modified release formulation, Presendin, has been developed for the treatment of IIH.

Byetta has a known issue of rapid elimination of the product when given to humans, and because of this it needs to be administered twice daily to achieve its pharmacological effects. The data on file from the IIH Pressure trial has shown that in patients with IIH, exenatide administered twice daily was well tolerated and produced a positive effect on reducing CSF pressure. However, it is considered that the immediate release formulation of exenatide is not ideal for treating patients with IIH on a long-term basis. Presendin has been developed as a modified release formulation to allow for a reduction in dosing frequency to once weekly.

This trial is designed to investigate the efficacy and safety of a modified release formulation of exenatide (Presendin) in patients with IIH.

Intracranial pressure

IIH is a debilitating condition characterised by raised ICP, which is clinically measured by LP [Mollan, 2018]. The units for measurement of LP are cm CSF and cm H_2O and these should be thought of as interchangeable and reflect the measurement of the height of the CSF column at LP. Lumbar puncture is conducted to make a diagnosis of IIH. Lumbar puncture may be conducted in a clinical setting during the disease course to both monitor and treat the condition. Frequent therapeutic LPs are no longer recommended by the International IIH guidelines [Mollan, 2018]. This is because LP can be traumatic for patients and can occasionally cause significant complications (meningitis, spinal haematoma, pain) [Wright, 2012]. Hence, unnecessary LP's should be avoided. In some patients LP can alter other outcome measures, including measurements of papilloedema and headache [Yiangou, 2019]. Hence ideally, LP should be performed after these measures and symptoms have been assessed. Lumbar puncture can cause post-dural puncture headaches. The risk is 9-36% using a traumatic needle and 3-19% using an atraumatic needle [Wright, 2012]. Post-dural puncture headaches typically last less than a week but in some patients this can be longer [Yiangou, 2019]. Lumbar puncture pressure assessment of ICP reflects disease activity and is a useful and recognised outcome measure that has been utilised in other IIH trials [Markey 2020; Mollan 2021b].

Due to the invasive nature of LP, non-invasive measures of ICP are valuable. The majority of techniques historically evaluated as non-invasive surrogate measures of ICP lack sufficient quantification to be used clinically or in clinical trials. Optical coherence tomography (OCT) measures of the optic nerve have been shown to provide a useful surrogate measure to quantify changes in ICP [Vijay, 2020]. For example, at 12 months, Vijay *et al* showed that a change in optic nerve head height of 50 μ predicted a 5 cm CSF change in ICP [Vijay, 2020].

Visual Function

Perimetry is used to measure visual function in IIH clinical practice. This is assessed using a Humphrey Field Analyzer (program24-2 SITA standard) test. Patients are often unaware of their visual field loss until this becomes more severe and compromises daily activities. In patients with severe papilledema optic atrophy can develop (measured objectively as loss of the ganglion cell layer on OCT) and the loss of visual field becomes permanent. Patients at risk of rapidly progressive visual loss (also termed fulminant IIH) should receive emergency surgical intervention (most commonly a CSF shunt operation) [Mollan, 2018]. Patients requiring emergency surgery will not be recruited into this trial. Medical therapy is used to treat those IIH patients not requiring emergency surgical intervention and will be included in this trial. But it is expected that approximately 5-10% will go on to need more aggressive intervention.

Measuring visual function with perimetry has a number of challenges in IIH which need to be carefully considered. The visual field test is dependent on technician and patient performance and is prone to variability and inaccuracy [Cello, 2016; Wall, 2016]. Patients can perform poorly on automated perimetry [Cello, 2016], and there is a learning effect [Kutzko, 2000; Wall, 2016]. There are further confounding factors when considering interpretation of automated visual field testing in IIH. The high prevalence of functional vision loss, presenting as non-organic visual fields results in this disease, may bias trial outcomes [Kutzko, 2000; Ney, 2009]. Additionally, impaired executive function and attention deficits have been noted in IIH [Sørensen, 1986], and have been shown to impair performance of visual field testing in IIH [Grech, 2021].

The protocol has been designed with these challenges in mind and visual field testing performance will be assessed at trial entry with opportunity for repeated assessment in the setting of performance failure. The visual fields will be assessed at the visual reading centre.

Papilloedema by change in optic nerve head size measured by OCT

Papilloedema is a reliable sign of raised ICP [Dunn, 2002]. Change in papilloedema has been used by all the randomised control trials in IIH to date to determine clinical improvement [Ball, 2011; Wall, 2014]. Change in papilloedema has been graded by experts using the Frisén classification, although it is more reliably measured by OCT imaging [Ball, 2011; Wall, 2014]. Professional bodies and the literature endorse the use of OCT for monitoring papilloedema in IIH [Mollan, 2018].

Optical coherence tomography measures different aspects of the optic nerve. The optic nerve head size and retinal nerve fibre layer (RNFL) are measurements that both reflect swelling of the optic nerve and hence the extent of papilledema. Measures of macular volume can quantify the ganglion cell layer (GCL) which reflects axonal loss. Optic nerve head measures on OCT correlate with visual field sensitivity loss [Salgarello, 2001]. Analysis has shown that OCT measures of the RNFL significantly reflect changes in visual field perimetric mean deviation (MD) (for every 10µm increase in RNFL there was associated with a 0.6dB decrease in MD) [Rebolleda, 2009]. Optical coherence tomography measures of the macula volume have been shown to predict axonal loss of the optic nerve [Albrecht, 2017]. Most importantly, ganglion cell volume has been shown to significantly correlate with visual field MD [Vijay, 2020]. This indicates that the GCL can be measured to reflect visual function. In other neurological diseases OCT has also been found to measure neuronal loss and correlated with visual loss [Petzold, 2010]. In summary, OCT assessment of the optic nerve and GCL represent objective measures of papilledema and optic nerve axons which determine visual function.

The scan quality can be compromised if the automated software segmentation of the OCT is not accurate. This occurs particularly in those optic nerves with more pronounced papilloedema [Aojula, 2018]. Hence the quality and segmentation of all OCT scans will be assessed by the visual reading centre and repeated if of insufficient quality.

Headache

Headache is the predominant presenting feature in IIH [Mollan, 2019a]. Patient morbidity is high because of disabling headaches and they have been found to be the key driver for poor quality of life [Mulla, 2015; Digre, 2015]. Research into headache treatments were endorsed as clinically relevant by a priority setting partnership which included the opinions of the patients' carers and physicians [Mollan, 2019c].

It has been well documented that headache characteristics in IIH are typically migraine-like (up to 90%) [Mollan, 2019b; Mollan 2021a]. The headache location can be halo-cranial, frontal, temporal or parietal with features including nausea, throbbing pain, photophobia and phonophobia [Yri, 2015]. A Danish trial of 44 IIH patients noted that 82% of patients had migraine-like attacks [Yri, 2014]. A prospective trial in 52 IIH patients in the UK characterised 80% of headaches as migraine-like [Yiangou, 2019]. As reported by the Idiopathic Intracranial Hypertension Treatment Trial, US, the headache phenotype was recorded as migraine or probable migraine in 68% of 144 patients with active IIH [Friedman, 2017]. A retrospective trial in Iran in 68 IIH patients characterised migraine-like headaches in 63% [Sina, 2017]. Other headache characteristics are typically tension-type or unclassified [Mollan, 2019b].

Hence whilst IIH headaches are not diagnostically the same as migraine according to the International Classification of Headache Disorders, 3rd edition Beta, they are very similar in character [Olesen, 2018]. The International Headache Society core outcomes for migraine are therefore applicable to IIH headaches [Tassorelli, 2018].

Headache in active IIH is driven by ICP. This is evidenced by the fact that removal of CSF fluid results in improved headache severity. In a prospective cohort study, headache severity improved in 71% following a standardised LP [Yiangou, 2019]. Ninety-five percent of IIH patients had improvement in headache symptoms at 1 month following shunt placement [Daou, 2020]. Weight loss leading to reduction in ICP also significantly reduced headache [Sinclair, 2010].

Medications that reduce ICP have been shown to modulate headache. In an open label trial using topiramate and acetazolamide, both of which are known to modulate ICP [Scotton, 2019], relief of headache was reported after a mean treatment period of 3.75 months in the topiramate group and 3.3 months in the acetazolamide group [Çelebisoy, 2007].

Importantly, headache measures (severity and monthly headache days) in IIH significantly correlate with changes in ICP [Mollan 2021a]. The IIH weight trial [Mollan, 2021b], a randomised controlled parallel group multicentre trial in the United Kingdom, investigates weight management methods in IIH. Participants with active IIH (evidenced by papilloedema) and a body mass index (BMI) ≥35kg/m^2 were recruited. The primary outcome was ICP as measured by LP opening pressure at 12 months, with secondary outcomes of ICP at 24 months and headache outcomes at 12 and 24 months. Headache severity was correlated with ICP at baseline; change in headache severity and monthly headache days correlated with change in ICP at 12 months. Importantly those with the greatest reduction in ICP over 12 months had the greatest reduction in headache frequency and severity. This implies that treatment of ICP should improve headache in IIH.

The following headache outcomes are clinically relevant and are recommended by the American Headache Society [American Headache Society] and International Headache Society to identify patients who are benefiting from treatments. Headache outcomes are derived from a 28-day diagnostic headache diary. This is used in clinical trials to prospectively collect daily information on headache occurrence, severity, associated symptoms, and use of acute analgesic medications.

Although a headache diary is typically over 28 days, for IIH headache it was felt unethical to have patients off treatment for this more prolonged period during screening due to the real risk of visual loss. Headache diaries designed to measure headache frequency have successfully utilised over shorter time periods in previous IIH trials and noted to be representative [Mollan 2021b]. Hence the baseline headache frequency will be calculated over 1 week as has been done in other trials.

Monthly headache days

Monthly headache days (MHD) will include 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 require acute headache analgesia. This is the most relevant and objective measure of headache.

Moderate to severe monthly headache days

A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications. This outcome captures the more disabling headaches.

Moderate to severe MHD was recently reported as the primary endpoint in a prospective open label study providing evaluation of the effectiveness of erenumab, a calcitonin

gene-related peptide (CGRP) monoclonal antibody, to treat headaches in IIH patients [Yiangou, 2021]. It is also used to measure headache in other secondary headache conditions such as persistent post traumatic headache [Aojula 2018; Ashina, 2020].

Headache responder rate (≥50% reduction in MHD)

Headache responder rate (≥50% reduction in MHD) is the proportion of patients achieving at least 50% reduction in the mean number of MHD, of any intensity, from baseline to the defined trial end point. This criterion is clinically relevant as it is used as an empirical review for continuing or discontinuing headache therapy [Diener, 2020]. Responder rates can be used in meta-analyses of placebo controlled randomised controlled trials.

Headache responder rate (≥50% reduction in moderate to severe MHD)

Headache responder rate (≥50% reduction in moderate to severe MHD) is the proportion of patients achieving at least 50% reduction in the moderate to severe MHD from baseline to the defined trial end point. It is well recognized that 50% responder rates may not fully capture the benefits of treatment [Matharu, 2017]. For example, a patient may improve from a disabling 20 severe headache days per month to 11 moderate headache days per month. Despite this considerable clinical benefit, such a patient would not be considered a responder because headache days were not reduced by ≥50%, and as a result might lose access to beneficial treatment. Hence, responder rates of ≥30% are also important [Vernieri, 2019]. In IIH, a disorder of chronic severe headaches, a clinically meaningful treatment responder rate has not been definitively established, although the International Headache Society Clinical Trials Subcommittee has suggested the use of a ≥30% reduction from baseline for chronic migraine.

Headache severity

Headache severity is an important measure and impacts quality of life. It is vital to consider some treatments which benefit headache may not reduce the MHD but if the severity is markedly improved this will lead to great overall functional benefit to the patient and is clinically relevant [Silberstein, 2008]. Recording the decrease in intensity is an indicator of reduced disability, which is clinically meaningful.

Monthly use of acute headache rescue medications

Use of acute headache analgesics reflects a judgement of the inefficacy of the test treatment; hence it is a helpful secondary outcome. In Sinclair *et al.* reduction in analgesic days was significant and associated with clinical remission of IIH [Sinclair, 2010]. Additionally, a high portion of IIH, up to 48% [Yiangou, 2021] have medication

overuse and medication overuse headache, and reduction in analgesic days mitigates these. Reduction in monthly use of acute headache analgesic is an additional endpoint that contributes to clinically meaningful results.

Quality of life in IIH

IIH has a detrimental effect on all aspects of the patient's quality of life; the majority of which is driven by headache [Kleinschmidt, 2000, Mulla, 2015; Daniels, 2007; Digre 2015]. IIH also impacts visual function with PMD correlating with quality of life [Bruce 2016]. Patient reported outcomes in clinical trials are essential not only to permit health technology assessments and cost effectiveness analysis, but also as key outcomes for a therapy's effectiveness [Deiner, 2019]. There is currently no IIH disease specific quality of life outcome measure.

Whilst there are differences in the choice of the tools used in the trials, they all commonly used the short-form 36 health survey (SF-36) [Mollan, 2021, Wall, 2014, Digre, 2015; Bruce, 2016; Ball, 2011]. The physical component score of the SF-36 has been shown to correlate significantly with changes in ICP [Grech 2021]. The EuroQol –5 dimension (EQ-5D-5L) [Euroqol, 1990] is typically employed for health technology assessments and cost effectiveness [Ottridge, 2017; Ball, 2011]. Using the EQ-5D-5L in isolation may lack sensitivity as compared to the SF-36 for IIH. The National Eye Institute Visual Function Questionnaire-25 and 10-item supplement [Mangione, 2001] has also been utilised to assess visual related quality of life in IIH and is associated with improvement in visual field [Bruce 2016; Mangione 1998; Raphael 2006]. The 10-Item neuro-ophthalmic supplement was found to be significantly discriminating in a previous IIH drug trial [Wall 2014].

1.1.1. Name and Description of the Investigational Product

Patients will receive active treatment, Presendin, or matching placebo.

Presendin is a modified release formulation of exenatide. Exenatide is a GLP-1 receptor agonist currently used in the management of type 2 diabetes. Presendin consists of a drug part (white or greyish white powder in a clear vial) and a diluent part (colourless liquid in a pre-filled syringe). The drug part is suspended in the diluent part solution and administered as a suspension. The patient or responsible person will be responsible for rehydrating the product for injection. Presendin is administered as a once weekly SC sustained-release injection containing 2.0 mg exenatide. Matching placebo will also be supplied as 2 parts, as visually identical vial and pre-filled syringe. The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. Placebo is administered once weekly as a SC injection.

1.1.2. Non-clinical Studies

Exenatide, the active ingredient of Presendin, has been previously developed and licensed as Byetta for the treatment of type 2 diabetes. A wealth of historical toxicological and pharmacological safety data is available in the public domain. Please see the Investigator's brochure for data from rat and mouse studies which have investigated the Presendin formulation of exenatide.

In vitro and *in vivo* data suggests that the choroid plexus, the CSF secreting structure in the brain, contains GLP-1 receptors [Ast 2020]. Preclinical studies in rodents demonstrate that GLP-1 agonists can regulate cerebrospinal fluid dynamics and reduce ICP [Botfield, 2017].

Nonclinical pharmacology studies have shown that exenatide and GLP-1 agonists bind to and stimulate GLP-1 receptors equipotently. Due to the ability of exenatide to affect fluid homeostasis in the kidney, it was investigated for its potential to modulate CSF secretion and reduce ICP in rats. A single SC injection of exenatide rapidly (within 30 minutes) reduced ICP and maintained lower ICP for 6 days of dosing, suggesting that GLP-1 receptor agonists could provide an alternative treatment for conditions with raised ICP [Botfield, 2017].

Exenatide was subjected to full toxicological assessments during its nonclinical development programme, details of which are publicly available in the Byetta® Product Monograph, 2019 and the FDA Pharmacology Review, June 2004 (Section 15). In summary, no lethality or serious toxicity was observed in mice, rats and monkeys following single doses up to 1500 µg/kg, 3000 µg/kg and 5000 µg/kg respectively. In repeat-dose toxicity studies decreased body weight gain and food consumption, a known pharmacological effect of exenatide, were observed in all studies. Exenatide caused no mortality or target organ toxicities in mice, rats and monkeys at doses up to 760µg/kg/day (182 days), 250 µg/kg/day (91 days), or 150 µg/kg/day (273 days) respectively. Reproductive toxicity data from animal studies showed that Byetta had a toxicological effect on foetal development at three times the human exposure levels in treatment of diabetes. A summary of the findings of the exenatide toxicological assessment programme is presented in the Investigator Brochure for Presendin.

1.1.3. Clinical Studies

Exenatide has undergone extensive healthy volunteer studies and clinical trials for over 15 years. It is licensed as a formulation for SC injection to be used in conjunction with diet and exercise to improve glycaemic control in adults with type 2 diabetes. Details of the trials conducted on exenatide, SC injection formulation, are presented in the Byetta Product Monograph (Section 15). Data from these studies are notable as the dose of exenatide to be used in the indication of IIH is intended to produce exposure levels not

exceeding those experienced by patients receiving Byetta. It is anticipated that the proposed therapeutic dose of exenatide, in the modified release formulation Presendin, for treatment of IIH will be within the approved dose range of Byetta, achieving a level of total systemic exposure comparable with the immediate release Byetta formulation. Therefore, safety data available from the Byetta clinical development program are considered relevant and supportive of exenatide development in IIH.

The efficacy of exenatide (Byetta) was evaluated in a Phase 2 randomised, placebo controlled, double-blind trial of exenatide in patients with active IIH (IIH:Pressure Trial). Sixteen patients with a diagnosis of active IIH (LP opening pressure >25 cm CSF and papilloedema) were identified and recruited to the trial. Participants had a telemetric ICP monitor implanted and were randomised to either exenatide (first dose was 2. 0 mcg followed by 10 mcg BD sub-cutaneous) or a matched placebo; allocation was 1:1. The treatment duration was 12 weeks. The trial was powered to seek significance to at least alpha < 0.1 and power at least 80% using equal group sizes. Data was analysed by hierarchical regression analysis. 16 participants were recruited, 15 were randomised and completed the study. At baseline the mean age was 28 ± 9 years, BMI 38.1 ± 6.2 kg/m2, ICP 23.5 ± 3.9 (equivalent to 32.0 ± 5.3 cm CSF). The primary outcome, change in intracranial pressure between arms, was significant: at 2.5 hours -4.2 ± 2.1 mmHg (equivalent to 5.7 ± 2.9 cm CSF), p=0.04, at 24 hours -4.7 ± 2.1 mmHg (equivalent to 6.4 ± 2.9 cm CSF), p=0.03, and at 12 weeks -4.1 ± 2.2 mmHg (equivalent to 5.6 ± 3.0 cm CSF), p=0.05. A significant reduction in monthly headache days was also observed amongst those on exenatide (-7.7 ± 9.2, p-0.069). LogMar visual acuity also significantly improved in the exenatide treated arm (-0.1 ± 0.05, p=0.036). No significant weight loss was observed in either arm and hence weight change is unlikely to have contributed to the reduction kin ICP observed. Exenatide was safe and well tolerated: no treatment related SAE's were reported, 8 adverse events were reported in those taking exenatide. The most frequent adverse event, amongst those taking exenatide, was nausea (7 reports), the majority of these were mild and all reports were self-limiting. There were no patient withdrawals due to adverse events.

1.1.4. Trial Conduct

This trial will be conducted in accordance with the requirements of this document (the Clinical Trial Protocol), the Trial Reference Manual and also in accordance with the following as per country specific requirements:

- Declaration of Helsinki (revised version of Fortaleza, Brazil, 2013)
- The International Council on Harmonisation harmonised tripartite guideline regarding Good Clinical Practice (E6 R2, November 2016)

- The United Kingdom Statutory Instrument 2004 No. 1031 and UKSI 2006 No.1928
- European Union Directives 2001/20/EC and 2005/28/EC
- United States Code of Federal Regulations Title 21
- The Australian Therapeutic Goods Act, 1989, amended December 2020 and Therapeutic Goods Regulations, 1990, amended January 2021
- Other country specific laws and regulations
- Any amendments to these regulations

1.2. Risk/Benefit Assessment

Current treatments for IIH have limited efficacy and can cause disabling side effects. Acetazolamide, the most commonly used drug (off licence) has a high side effect profile (48% discontinued in a clinical trial due to intolerable side effects) [Ball, 2011]. Although IIH is a rare condition, incidence is rising with rising obesity trends. Improving IIH morbidity with new therapeutics is clearly an unmet need.

Safety data for Presendin (exenatide) is based on the IB (Peptron Inc.). Warnings include pancreatitis, hypoglycaemia when used in combination with a sulfonylurea, renal impairment, severe gastrointestinal disease and hypersensitivity.

Invex Therapeutics has considered these warnings and has defined eligibility criteria to ensure patient safety is paramount. As such patients with known contraindications to GLP-1 agonists, such as pancreatitis, ketoacidosis, severe gastrointestinal disease and renal impairment, will not be included. Additionally, diabetic patients receiving glucose lowering medication will be excluded.

An Independent Adjudication Committee (IAC), as described in Section 14.5, will assist the Investigators when required with the eligibility criteria of the patients to be enrolled to ensure patient safety and the efficacy of the trial.

The most common adverse reactions experienced with exenatide are nausea, hypoglycaemia (only when used with other glucose lowering drugs, but these patients are excluded from the trial), vomiting, diarrhoea, feeling jittery, dizziness, headache and dyspepsia.

Patients receiving the active treatment during the randomised period may benefit by experiencing an improvement in their IIH symptoms, although this cannot be guaranteed.

2. OBJECTIVES

2.1. Primary Objective

To determine the efficacy of Presendin administered subcutaneously once weekly for 24 weeks to patients with IIH, as determined by change in ICP, as measured by LP at baseline and at 24 weeks.

2.2. Secondary Objectives

To determine the effect of Presendin on change in:

- Perimetric Mean Deviation as measured by Humphrey Visual Field analysis (24-2 SITA-Standard)
- Papilloedema by change in optical coherence tomography (optic nerve head size and retinal nerve fibre layer (RNFL) thickness)
- Monthly headache days (MHD)
- Moderate to severe monthly headache days
- Headache responder rate (≥50% reduction in monthly headache days)
- Headache responder rate (≥50% reduction in moderate to severe monthly headache days)
- Headache severity
- Monthly use of acute headache analgesic medications
- Visual acuity
- Treatment failure

2.3. Safety Objective

To determine the safety of Presendin administered subcutaneously once weekly as determined by vital signs, the occurrence of adverse events (AEs), electrocardiogram (ECG) and routine laboratory assessments.

2.4. Exploratory Objectives

To determine the effect of Presendin on:

- Ganglion cell layer thickness
- Retinal nerve fibre layer thickness
- Headache responder rate: ≥30% reduction in monthly headache days

- Headache responder rate: ≥30% reduction in moderate to severe monthly headache days
- Patient Reported Outcomes
- Body Mass Index
- Body Weight
- Health Utilisation

3. ENDPOINTS

3.1. Primary Endpoint

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

3.2. Secondary Endpoints

- Perimetric Mean Deviation
- Optic nerve head size
- Retinal nerve fibre layer (RNFL) thickness
- The number of monthly headache days (MHD). Monthly headache days will include all headache days, defined as those with an onset, continuation or recurrence, any severity or phenotype of headache, lasting at least 30 minutes or which require acute headache analgesia.
- Number of monthly moderate to severe headache days. A moderate/severe headache day will be defined as a day with moderate or severe pain that lasts at least 4 hours or that requires acute headache analgesic medications
- Responder rate monthly headache days (defined as a ≥50% reduction)
- Responder rate moderate to severe monthly headache days (defined as a ≥50% reduction)
- Headache severity (assessed by 11-point Numeric Rating Scale [NRS], 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
- Treatment failure, defined as initiation of either medical therapy or a surgical intervention to lower ICP.*

*criteria defined in rescue therapy section 10.1.1

3.3. Safety Endpoints

- Vital Signs
- Adverse events: Treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), serious adverse events (SAEs)
- Resting 12-lead electrocardiogram
- Routine laboratory assessments (haematology, biochemistry and urinalysis)

3.4. Exploratory Endpoints

- Ganglion cell layer thickness
- Responder rate monthly headache days (defined as ≥30%)
- Responder rate moderate to severe monthly headache days (defined as ≥30% reduction)
- Patient Reported Outcomes (PRO):
  - Visual Function Questionnaire-25 and 10-item supplement
  - Headache Impact Test-6
  - 36-item short form survey
  - EuroQol -5 dimension -5 level survey
  - Patient Global Impression of Change
- Body Mass Index
- Body Weight
- Health Utilisation

4. TRIAL DESIGN

4.1. Summary of Trial Design

4.1.1. Trial Design

This will be a randomised, placebo-controlled, double-blind, multi-centre clinical trial in approximately 240 randomised patients with IIH.

The trial will begin with a 1-week screening period. Although a headache diary is typically over 28 days, it was felt unethical to have patients off treatment for this more prolonged period. Headache diaries designed to measure headache frequency have been successfully utilised over shorter time periods in previous IIH trials and noted to be representative [NORDIC, 2018; Mollan, 2021b]. Hence the baseline headache frequency will be calculated over 1 week. Patients will be provided with training on the self-administration of the trial medication from the site trial coordinator and provided with a leaflet to take home at the screening visit. Patients will be asked to self-administer placebo during the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable with self-administration will be deemed screen failures, and not be randomised into the trial. The purpose of the screening period will be to establish baseline measurements and assess trial eligibility.

The screening period will be followed by a 24-week randomised double-blind treatment period in which patients will be randomised (1:1) to receive a SC dose of either Presendin (containing 2mg of exenatide (active group) or matching placebo (placebo group), self-administered once weekly.

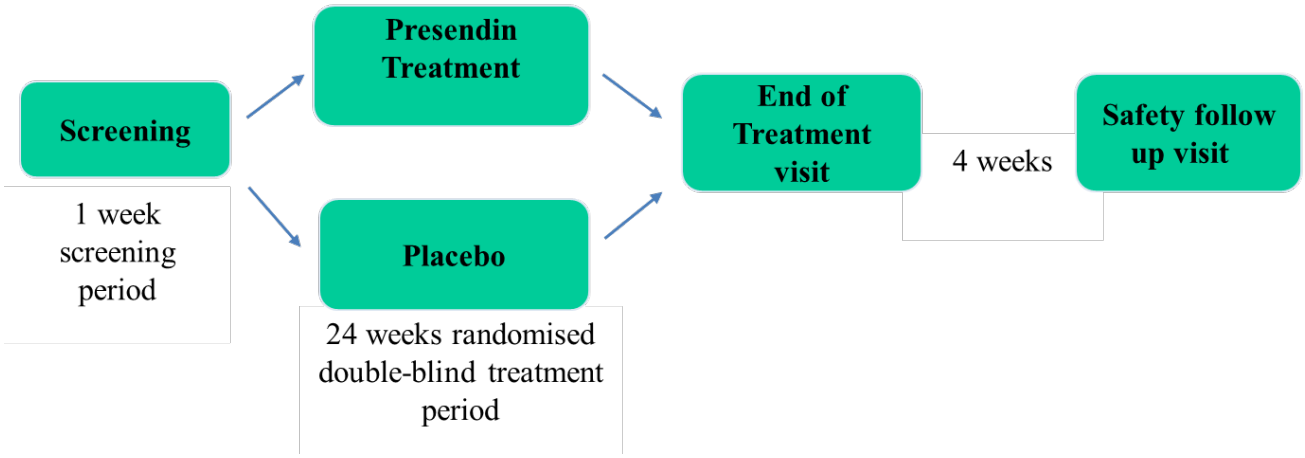
At the end of the randomised treatment period (week 24), all patients will have an end of treatment clinic visit. Four weeks after the end of that treatment visit, an end of trial safety follow-up telephone visit will be performed. In the event of any abnormal safety assessments or ongoing adverse event(s) identified at end of treatment; for example, an abnormal ECG or abnormal routine laboratory results, this visit may be performed at the clinic and a safety follow-up performed as appropriate.

The duration of the randomised treatment period was felt to be appropriate as the previous phase 2 trials of Exenatide in IIH demonstrated efficacy by 3 months. Additionally, an alternative off label drug used in IIH (acetazolamide) was evaluated over a 6-month period. Hence efficacy is relevant over this time frame. A longer period of randomisation would not be ethical if patients were expected to remain on placebo for 12 months as this could place their overall health at risk.

Assessments will be performed as outlined in Table 1.

A schematic diagram of the trial can be seen in Figure 1.

Figure 1: Schematic Diagram



4.1.2. Randomisation and Blinding

At the end of the Screening period, eligible patients will be randomised to receive either Presendin or matching placebo in a 1:1 ratio using a computer system to generate randomisation codes.

Investigators and other site personnel, patients, contract research organisation and Sponsor personnel will be blinded regarding the treatment during the randomised period. Only designated unblinded staff, not involved in the operational conduct of the trial, will be aware of the randomisation codes.

The placebo will have the same appearance and reveal no differences, during administration, to either the Investigator or the patient.

4.1.3. Duration of Patient Participation

The duration of the trial for each patient will be up to 29 weeks, which includes a 1-week screening period, a 24-week randomised treatment period and a treatment follow-up period of 4 weeks.

4.2. Stopping Rules

4.2.1. Trial Stopping Rules

There are no trial-specific stopping rules. The Sponsor maintains the right to stop the trial at any point. If this is done, then the Sponsor will provide the Investigators with the rationale for such early termination.

4.2.2. Individual Stopping Rules

Patients will be withdrawn from the trial medication if they are unable to tolerate the trial medication and will continue to attend trial visits as per protocol. See Section 11 for further details. A Data Safety Monitoring Committee (DSMC) will be involved in decisions for patient safety (Section 14.6).

4.3. End of Trial

The end of trial is defined as last patient last visit.

5. TRIAL POPULATION

5.1. Number of Patients

It is anticipated that approximately 300 patients will be required to enter the screening phase for 240 patients to be randomised into the treatment phase.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

Patients must not be enrolled unless they meet all the following criteria:

1. Age ≥18 years at the time of consent
2. Diagnosis of IIH by consensus criteria (see Section 16.1, Appendix 1), including normal structural brain imaging (excluding features of raised intracranial pressure and incidentalomas), including either magnetic resonance venography or computed tomographic venography to exclude thrombosis and no evidence of a secondary causes of raised intracranial pressure
3. Lumbar puncture opening pressure ≥ 25 cm H_2O CSF at baseline
4. Screening commenced no more than 4 weeks after the diagnostic LP
5. Presence of bilateral papilloedema established from OCT imaging by the reading centre (Frisén grade ≥1). Where there is uncertainty fundus photography and/or ultrasound scan (B scan) of the optic nerve should be conducted for evaluation by the reading centre
6. Perimetric mean deviation (PMD) (with mild/moderate visual loss) -2 to -7 decibels (dB)
7. Reproducible visual loss present on automated perimetry including no more than 15% false positive responses (reliability confirmed by the reading centre)

8. Greater than 3 days headache over the 7-day period prior to screening and also the patient must meet this criterion during the 7-day screening period
9. Females of childbearing potential must have a negative pregnancy test and must agree to use a highly effective birth control method (failure rate less than 1% per year when used consistently and correctly – see Section 16.7, Appendix 7 for further details) during the whole trial duration including the last follow-up visit (12 weeks after ceasing drug). Female patients who are lactating must agree to stop breast-feeding. Or female patients of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory])
10. Male patients with a female partner of childbearing potential must commit to practice methods of contraception (e.g., condom, vasectomy) and abstain from sperm donation during the trial including the last follow-up visit (12 weeks after ceasing drug). Their partners, if they are women of childbearing potential, must agree to practice contraception and to use a highly effective method of contraception during the trial, including the last follow-up visit (12 weeks after ceasing drug)
11. Greater than 2 weeks prior to screening since COVID-19 vaccination (for patients that have received the Covid-19 vaccination)
12. Able to provide written informed consent

5.2.2. Exclusion Criteria

Patients must not be enrolled if they meet any of the following exclusion criteria:

IIH related exclusions criteria:

1. Presence of venous sinus thrombosis on brain imaging by either magnetic resonance or computerised tomographic venography
2. Previous IIH surgery including CSF shunt, optic nerve sheath fenestration or dural venous sinus stent or sub-temporal decompression
3. Previous bariatric surgery within the last 3 months or intention during the trial
4. Abnormal neurological examination (aside from papilloedema and consequent visual loss or sixth nerve palsy or palsies)
5. Treatment to lower ICP within 1 week prior to screening visit (e.g., acetazolamide, topiramate, diuretics, glucocorticoids (oral dexamethasone and oral prednisolone))

Vision related exclusion criteria:

6. Patients with a past ophthalmic history or diseases causing visual loss, other than cataract extraction, or pre-existing optic disc or retinal diseases that may (in the opinion of the Independent Adjudication Committee [IAC]) affect interpretation of the visual outcomes (e.g., ischaemic optic neuropathy, optic neuritis, pronounced optic disc drusen, optic atrophy, retinal, or choroidal diseases)
7. Existing clinically relevant optic atrophy which, in the opinion of the IAC, may affect interpretation of the visual outcomes
8. Refractive error > +/- 6.00 sphere or > +/- 3.00 cylinder in either eye. In addition, participants with myopia of >-6.00 D sphere but less than or equal to -8.00 D sphere are eligible if the subject wears a contact lens for all perimetry examinations with the appropriate correction
9. Poor Humphrey Visual Field (HVF) test quality which, in the opinion of the IAC, may affect interpretation of the HVF that is not rectified through repeat testing

Headache related exclusion criteria:

10. Has received botulinum toxin or monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or CGRP antagonist injections within the last 4 months for headache or has intention to initiate such injections during the trial
11. Has undergone nerve block (occipital or other) in the head or neck within the last 4 weeks or has intention to undergo nerve block in the head or neck during the trial
12. Does not complete ≥6 days of electronic/paper trial diary during the 7 day screening period

Other exclusion criteria:

13. Untreated documented obstructive sleep apnoea with historically recorded apnoea-hypopnea index greater than 15
14. Allergy/known hypersensitivity to the active substance and/or excipients of the investigational product
15. Has known contraindications to GLP-1 receptor agonists (e.g., ketoacidosis, severe gastrointestinal disease, pancreatitis, renal impairment) which, in the opinion of the investigator or the IAC, may affect the safety of the patient
16. Currently taking or has received a GLP-1 receptor agonist within the last 4 weeks
17. Using any glucose-lowering medication

18. Currently taking warfarin
19. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥2x the upper limit of normal (ULN), total bilirubin ≥1.5x ULN, or alkaline phosphatase (ALP) ≥1.5 ULN at screening (Note – patients with elevated total bilirubin are not excluded if they meet criteria for Gilbert's syndrome, including: bilirubin is predominantly indirect [with normal direct bilirubin level]; and ALT, AST and ALP ≤1x ULN)
20. Kidney disease (as defined by serum cystatin C-based estimated glomerular filtration rate [eGFR] <55 mL/min/1.73 m^2, calculated at investigator site)
21. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the central laboratory and confirmed by a single repeat, if deemed necessary: *Haemoglobin <10 g/dL (<100 g/L); Platelet count <75 x 10^9/L (<75,000/mm^3)*
22. Using recreational (including cannabidiol) or illicit drugs (including marijuana) at the time of signing the informed consent, or recent history (within the last year) of drug or alcohol abuse or dependence according to the DSM-5 criteria, that in the opinion of the investigator puts the patient at risk
23. Is unable to self-administer the trial medication (or unable to administer trial medication with support) after receiving training during the Screening period
24. History of any clinically significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the trial or influence the results or the patient's ability to participate in the trial
25. Has participated in any other interventional trial within 1 month prior to the screening visit. COVID vaccination trials are not considered an exclusion criteria provided the COVID vaccination has occurred > 2 weeks prior to screening visit.
26. Is pregnant or breastfeeding

6. TRIAL ASSESSMENTS AND PROCEDURES

6.1. Procedures at Each Visit

Trial procedures and timings are presented in the Time and Events Table, Table 1.

No procedures should be performed prior to obtaining informed consent. All visits (except telephone call visits) should be performed at the clinic. Should a clinic visit not be possible, due to a patient self-isolating, the visit will be conducted at the earliest opportunity and will not constitute a protocol deviation.

6.1.1. Visit 1 Screening

The screening period must be a minimum of 7 days, up to a maximum of 10 days. Visit procedures can be performed in a single visit or over a number of visits during the screening period. Ideally all screening procedures should be performed on the same day.

- Obtain patient's written informed consent
- Eligibility criteria
  - Including confirmation that diagnostic LP occurred within the last 4 weeks with an opening pressure ≥ 25 cm CSF in lateral decubitus position
- Demographics (sex, age and ethnicity)
- Medical and ophthalmic history
- Concomitant mediation history
- Headache history
- Headache preventative medication review
- Headache diary dispensed and diary training – to be performed on first day of screening.
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Height, body weight and BMI
- Full physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Visual Assessments to both eyes
  - Optical coherence tomography Imaging

  Frisén grading will be inferred from the OCT imaging by the visual reading centre. Where there is uncertainty, fundus photos and or ultrasound scan (B scan) of the optic nerve should be conducted for evaluation by the reading centre
  - Humphrey Visual Field (24-2 SITA-Standard)
  - Visual Acuity (LogMAR score)

  Visual assessments should be uploaded to the visual reading centre at the earliest opportunity during the visit to ensure satisfactory quality. Quality reports would be received within 24 hours and those visual tests failing to meet criteria would be

repeated at the earliest opportunity with in the screening timeframe (up to 7 days) at an unscheduled visit

- Laboratory assessments
- Trial medication training. Patients will be asked to self-administer 1 dose of placebo at the screening visit to ensure they are comfortable with self-injection. Patients who are not comfortable will be excluded

6.1.2. Visit 2 Baseline

- Review eligibility criteria
- Concomitant medications review
- Headache preventative medication review
- Review headache diary (Patient must meet required number of headache days as per inclusion criteria. If the headache diary exceeds 7 days, then eligibility will be based on the last 7 days of the screening period, i.e. the 7 days prior to randomisation visit)
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse events review
- Targeted physical examination
- Urine pregnancy test (for women of childbearing potential)
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
        - Optical coherence tomography Imaging will be used to confirm equivalent or increased papilloedema from visit 1. Where papilloedema has reduced, Frisén grading must be re-performed (by the visual reading centre) to confirm eligibility prior to randomisation
    - Humphrey Visual Field (24-2 SITA-Standard)
        - A quality assessment should take place at site to ensure no more than 15% false positives in line with eligibility criteria. Where the visual field quality lies outside this parameter it should be repeated

- Visual Acuity (LogMAR score)

  Visual assessments should be uploaded to the visual reading centre at the earliest opportunity during the visit. If the quality is insufficient they should be repeated at an unscheduled visit

- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Laboratory assessments
- Pharmacokinetic sampling (pre-dose)
- Anti-Drug Antibodies (ADA) blood sampling
- Patient randomised
- Trial medication training
- Trial medication dispensed and first dose self-administered at clinic. Patients will then be instructed to administer subsequent doses once weekly.

6.1.3. Visit 3 Telephone call

All patients will receive a telephone call at visit 3 to conduct headache preventative medication review, check for any AEs or changes in medication, procedures outside of protocol, health utilisation, to remind them to complete their diary and to answer any questions they may have on administration or storage of the trial medication.

6.1.4. Visits 4, 5, 6, 7, 8 and 9 Clinic visits

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI (not visit 4)
- Adverse event review
- Targeted physical examination (visit 6, 8 and 9 only)
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram

- Visual Assessments to both eyes
  - Optical coherence tomography Imaging
  - Humphrey Visual Field (24-2 SITA-Standard)
    - A quality assessment should take place at site to ensure no more than 15% false positives. Where the visual field quality lies outside this parameter it should be repeated.
  - Visual Acuity (LogMAR score)

  Visual assessments should be uploaded to the visual reading centre at the earliest opportunity during the visit to ensure satisfactory quality. Quality reports would be received within 24 hours and those visual tests failing to meet criteria would be repeated at the earliest opportunity at an unscheduled visit.
- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary (not visit 4)
- Health Utilisation Form
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-Drug Antibodies blood sampling
- Trial medication dispensing (not Visit 4) and accountability -patients should be reminded by the trial site to self-administer the trial medication weekly and to return used and unused trial medication at clinic visits.

6.1.5. Visit 10

In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return.

Where more than one dose has been missed during the 4 weeks preceding visit 10, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days.

- Concomitant medication review

- Headache preventative medication review
- Headache diary review
- Vital signs (triplicate readings for blood pressure and heart rate will be taken at 1-minute intervals)
- Body weight and BMI
- Adverse event review
- Targeted physical examination
- Urine pregnancy test for women of child-bearing potential
- Electrocardiogram
- Visual Assessments to both eyes
    - Optical coherence tomography Imaging
    - Humphrey Visual Field (24-2 SITA-Standard)
    - Visual Acuity (LogMAR score)

  Visual assessments should be uploaded to the visual reading centre at the earliest opportunity during the visit to ensure satisfactory quality. Where the quality is insufficient the test should be repeated at the earlier opportunity.

  All visual imaging assessments should ideally be performed prior to LP.
- Lumbar puncture (within 7 days of last dose of trial medication)
    - Lumbar puncture to be performed after visual assessments
- Patient reported outcomes: VFQ-25 & 10-item supp, HIT-6, SF-36 and EQ-5D-5L in diary
- Health Utilisation Form
- Patient global impression of change question
- Laboratory assessments
- Pharmacokinetic blood sampling
- Anti-drug antibodies blood sampling
- Trial medication accountability

Where it is not feasible to conduct all of visit 10 procedures on the same day, these could be split provided visual assessments are performed before the LP and the patient remains on trial medication with the last dose within 7 days of the LP.

6.1.6. Visit 11 Follow-Up

This visit will be performed as a telephone call to conduct headache preventative medication review and check for any AEs or changes in medication. In the event of any abnormal safety assessments identified at the end of treatment, e.g., abnormal ECG, abnormal routine laboratory results or ongoing adverse events, this visit may be performed at the clinic to repeat or follow up safety assessments.

6.1.7. Unscheduled visit for repeat visual assessments

Optional visit for patients that perform visual assessments inadequately (OCT and/or HVF and/or LogMar) or where there is technical failure (more than 15% false positive response for HVF or OCT imaging not amenable to segmentation (even when manually corrected) which, in the opinion of the IAC, may affect interpretation of the OCT imaging). Imaging of eye in which there is inadequate performance only.

- Optical coherence tomography (as required)
- Humphrey Visual Field (24-2 SITA-Standard) (as required)
- Visual Acuity, LogMAR score (as required)

6.2. Trial Procedures

6.2.1. Screening Procedures

6.2.1.1. Demographics

The Investigator, or designee, should record the patient's sex, ethnicity, age, height, body weight and BMI at screening.

Ethnicity data will be collected in order to monitor any response differences in IIH disease progression/symptoms in different ethnicities.

6.2.1.2. Medical, Headache and Ophthalmic History

The Investigator, or designee, should record any ongoing co-morbidities and significant medical, headache and ophthalmic history along with the year in which such co-morbidities began (where known).

6.2.1.3. Reporting of Prior and Concomitant Medication

Concomitant treatment is any medication or therapeutic intervention being continued by the patient at trial entry and any new medication received during the trial. Prior treatment

includes previous medications, treatments and interventions received in the past but no longer ongoing.

For this trial, only relevant prior concomitant medications within the last 4 months will be recorded. These include:

- Headache preventative medications
- Intracranial pressure lowering drugs
- Botulism toxin or monoclonal antibodies targeting CGRP or CGRP antagonist injections
- Oral dexamethasone and oral prednisolone
- Nerve block (occipital or other) in the head or neck
- Glucose lowering medication
- Recreational drugs

At every visit the Investigator or a qualified designee will ask the patient about relevant concomitant medication.

No new medication should be started during the trial, unless medically necessary. The patient should be advised to consult the Investigator or designee before taking any prescribed or over-the-counter medications. In the case of headache preventative medications or ICP lowering medications please see details in the rescue therapy section. Acute headache analgesics are permitted and should be reported in the diary.

6.2.2. Safety Procedures

6.2.2.1. Physical Examination

A full physical examination will be performed at the screening visit. At a minimum the following will be assessed: ear, nose and throat, cardiovascular system, pulmonary system, skin, abdomen and neurological system. At all other time points a targeted (symptom directed) examination will be performed at the Investigator's discretion.

6.2.2.2. Twelve- Lead Electrocardiogram

Twelve lead ECGs should be performed at the times outlined in the Time and Events table (Table 1) in a standardized manner, i.e., after the patient has rested in the semi-supine position for at least 10 minutes. Measurements will be made using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, and QT intervals.

All ECG traces will be reviewed and signed by the Investigator or designee and any abnormalities will be marked as clinically significant or not clinically significant.

6.2.2.3. Vital Signs

Vital signs, including: systolic and diastolic blood pressure and heart rate, will be measured at the time points specified in Table 1.

Patients should rest in a supine position for 10 minutes before the vital signs are assessed. Three recordings will be taken and the average taken.

6.2.2.4. Laboratory Assessments

Blood and urine samples will be processed at the site. Routine biochemistry and haematology samples will be evaluated at the trial appointed central laboratory. PK, ADA and CSF samples will be stored at the central laboratory and evaluated at a qualified international laboratory. Details of handling and shipping are described in the Laboratory Manual.

6.2.2.4.1. Haematology

Blood for the assessment of haematology parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Total blood count; consisting of:
  - Red blood cells
  - Haematocrit
  - Mean cell volume
  - Mean cell haemoglobin
  - Mean cell haemoglobin concentration
  - Glycated haemoglobin (HbA1C)
  - Blood glucose (non-fasting)
  - Platelets
  - White blood cells
  - Neutrophils
  - Lymphocytes

- Monocytes
- Eosinophils
- Basophils

6.2.2.4.2. Clinical Chemistry

Blood for the assessment of clinical chemistry parameters will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed during the trial:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen
- Creatinine
- Total bilirubin
- Total protein
- Albumin
- Alanine transaminase
- Aspartate aminotransferase
- Alkaline phosphatase

6.2.2.4.3. Urinalysis

Urine samples will be collected at the times outlined in the Time and Events table (Table 1). The following parameters will be assessed at each time point:

- Glucose
- Ketones
- Specific gravity
- Blood
- pH
- Protein

- Urobilinogen

6.2.2.4.4. CSF

CSF sample from visit 10 LP will be retained for future potential analysis of disease and drug related biomarkers.

6.2.2.4.5. Pregnancy

Urine will be collected from female patients of childbearing potential at the times outlined in the Time and Events table (Table 1) to enable urine-based pregnancy tests to be performed. Female patients who are identified as being pregnant during the trial will be withdrawn from further treatment but will continue to attend safety follow-up visits.

The Investigator or designee should report any pregnancies in female patients to the Sponsor or designee, using the Pregnancy Report Form, within 24 hours. The contact details for reporting are:

[redacted]

Female patients or partners of patients who become pregnant should be followed until delivery, stillbirth or termination. The outcome of the pregnancy and, if applicable, the health of the baby, should be reported to the Sponsor using the Pregnancy Report Form.

6.2.2.4.6. Pharmacokinetic sampling

Pharmacokinetic sampling is to characterize the pharmacokinetics of exenatide after once weekly subcutaneous administration of Presendin at the times outlined in the Time and Events table (Table 1).

The primary purpose of the pharmacokinetic sampling is to characterize the steady state concentrations of exenatide. All actual sampling times and dosing times will be recorded.

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.4.7. Anti-drug Antibodies sampling

Anti-drug antibodies sampling will be performed in all subjects at the times outlined in the Time and Events table (Table 1).

Sampling and processing will be performed as described in the Laboratory Manual.

6.2.2.5. Adverse Events

Patients will be asked non-leading questions to assess how they are feeling at each clinic visit. Adverse events will be assessed and reported as outlined in Section 12.

6.3. Efficacy Procedures

6.3.1. Intracranial Pressure

Assessment of ICP will be measured by LP in the lateral decubitus position, according to LP standard operating procedure (SOP). Lumbar puncture will ideally be performed after visual assessments as outlined in the Time and Events table (Table 1).

Any additional LP procedures, outside of the protocol would constitute a protocol deviation and ideally should be discussed with the Investigator before the procedure is performed.

Non-protocol LPs should be recorded in the Case Report Form.

6.3.2. Visual Assessments

Visual assessments should be performed on both eyes. All visual assessments should be uploaded on the day of the visit at the earliest opportunity to the visual reading centre. In all cases the site is responsible for initial checks of data quality:

i. Humphrey Visual Field false positives <15%;
ii. Optical coherence tomography displays accurate segmentation (either through the automated software or manually corrected)

The visual reading centre will provide a definitive quality report and in some cases assessments will need repeating at the earliest opportunity.

6.3.2.1. Optical Coherence Tomography

Imaging may be acquired using Heidelberg or Cirrus platforms according to the OCT SOP. Key measures are optic nerve head size, RNFL and ganglion cell layer thickness.

- At screening OCT will be reviewed by the central ophthalmic reading facility to confirm eligibility.
- Frisén Grade will be inferred from the OCT imaging by the visual reading centre. During screening, where there is uncertainty a fundus photo and or ultrasound scan (B scan) of the optic nerve should be conducted for evaluation by the reading centre.

- Whilst optic disc drusen that effects the interpretation of the OCT imaging is an exclusion criterion, those with minimal optic disc drusen at screening identified on OCT by the central ophthalmic reading facility will be reported to the IAC to review and confirm eligibility.
- Any OCT with findings that suggest the patient may require rescue therapy will be prioritised and the report expedited to the IAC and site for review, to determine if rescue therapy is indicated.

6.3.2.2. Humphrey Visual Field

Visual field will be measured by Humphrey Visual Field analysis (24-2 SITA-Standard) according to PMD SOP.

- At screening HVF will be reviewed by the central ophthalmic reading facility to confirm eligibility
- Un-correctable poor performance (including >15% false positives) is an exclusion criterion. HVF can be repeated to obtain as assessment with reliable performance.
- Any HVF with findings that suggest the patient may require rescue therapy will be prioritised and the report expedited to the IAC and site for review, to determine if rescue therapy is indicated.

6.3.2.3. Visual Acuity

Assessment of corrected visual acuity will be recorded using a LogMAR scoring chart.

6.3.3. Headache Assessments

Patients will be provided with an electronic/paper diary at screening to complete during the course of the trial. Information collected will be used to assess the following headache parameters:

- Monthly headache days
- Monthly moderate to severe headache days
- Responder rate
- Monthly acute analgesic use
- Headache severity (11-point NRS)

6.3.3.1. Headache Preventative Medication Review

A review of any headache preventative medications taken by the patient will be undertaken at each clinic visit. If the Investigator alters the headache preventative medication, this will be considered rescue medication (Section 10.1.1) and the IAC consulted. This will be considered a protocol deviation. Use of headache preventative medication will be recorded at trial visits as outlined in the Time and Events table (Table 1).

Patients will record their acute headache analgesic use in their trial diary.

6.3.4. Patient Reported Outcomes

6.3.4.1. Visual related

Assessment of visual related quality of life will be derived from self-reported responses to the VFQ-25-10 item supp (see Section 16.5 Appendix 5).

6.3.4.2. Health-related

Assessment of health-related quality of life will be derived from self-reported responses using the following questionnaires:

- 36-item short form survey
- EuroQol -5 dimension -5 level survey

A Healthcare Utilisation Form will be completed by the trial site staff at clinic visits.

All questionnaires can be found in Section 16, Appendix 2 for SF-36 and Appendix 3 for the EuroQoL- 5D-5L survey.

6.3.4.3. Headache related Quality of Life

Assessment of headache-related quality of life will be derived from self-reported responses to the Headache Impact Test-6 questionnaire and performed at time points as outlined in the Time and Events table (Table 1). A copy of this questionnaire can be found in Section 16.4, Appendix 4.

6.3.4.4. Patient Global Impression of Change

The Patient Global Impression of Change will be conducted at visit 10, as outlined in the Time and Events table (Table 1).

It is a single item questionnaire using a seven-point verbal response scale to assess overall change in the patient's status since taking trial medication. A copy of this questionnaire can be found in Section 16.6, Appendix 6

6.3.5. Body Weight and Body Mass Index

The patient's body weight and BMI will be measured at the time points as outlined in the Time and Events table (Table 1).

The patient's height will be measured at Screening (shoes off).

7. SAFETY MEASURES DUE TO A GLOBAL CRISIS

The COVID-19 global pandemic presents numerous challenges to the conduct of ongoing clinical trials. In line with the FDA and European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (EMA, 2021), the following protocol considerations are provided to ensure patients safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain. Other unforeseen global crises may occur during the conduct of the study, similar to the COVID-19 global pandemic, in which case the following protocol considerations may also be applied.

Recognizing the flexibility required to manage the impact of the pandemic (or other global crisis) on this clinical study, additional details will be added to respective study manuals, project plan documents, and communicated to the investigative sites as needed. For any additional questions, the investigator should confer with the sponsor.

Number of Trial Patients

The evolving situation of the pandemic (or other global crisis) may result in a substantial number of patients' early withdrawal from the study, which could affect the data integrity of the study. Because of this risk, the sponsor may decide to recruit additional patients in the study, beyond the expected number, to mitigate such risk.

Study Visits

There are a number of on-site visits that would be required to ensure study validity. If there are local travel restrictions, isolation requirements, or the investigator determines it to be unsafe for patients to attend their scheduled study visits, the site staff may conduct certain visits via telemedicine (phone or video calls) to minimize patient risk as follows.

Screening Period

The following visit must be performed in person:

- Screening/Visit 1
  Note: To minimize direct, in-person contact between site personnel and patients, certain screening procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site.
  Specifically, the following procedures may be done remotely:
  - Informed consent (where applicable, per approved IRB/IEC process)
  - Demography

- Medical and ophthalmic history
- Concomitant medication history
- Headache history
- Headache preventative medication review
- Train and dispense headache diary
- Trial medication training

Randomised period

- Baseline (Visit 2)
  There are essential aspects to the baseline visit which must be performed in person.
  If the baseline visit is delayed the headache diary should utilise the preceding 7 days data. Where the visit is delayed by more than 10 days due to a global crisis the patient will be considered to have failed screening. Patients who screen failed due to the pandemic (or other global crisis) may be rescreened at a later time, if feasible.

  To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:
  - Concomitant medication review
  - Headache preventative medication review
  - Headache diary review
  - Adverse events
  - Patient reported outcomes
  - Health utilisation form

- Visit 4, 5, 6, 7, and 8
  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination

- Urine pregnancy test
- Electrocardiogram
- Optical coherence tomography imaging
- Humphrey Visual Field
- Visual acuity testing
- Laboratory assessments
- Pharmacokinetic sampling
- Anti-drug antibodies sampling

To minimize direct, in-person contact between site personnel and patients, certain procedures may be performed remotely via telemedicine. All other procedures should be done in-person while the subject is on-site. Specifically, the following procedures may be done remotely:

- Concomitant medication review
- Headache preventative medication review
- Headache diary review
- Adverse events
- Patient reported outcomes
- Health utilisation form

- Visit 10

  There are essential aspects to these visits which must be performed in person. Where this is not possible due to the pandemic or other global crisis the following components of the visit should be performed at the next available opportunity in line with the schedule of assessments table:
  - Vital signs
  - Body weight and BMI
  - Physical examination
  - Urine pregnancy test
  - Electrocardiogram
  - Optical coherence tomography imaging
  - Humphrey Visual Field
  - Visual acuity testing
  - Laboratory assessments
  - Pharmacokinetic sampling
  - Anti-drug antibodies sampling

- Lumbar puncture*

* Lumbar puncture to be performed after visual assessments. In the 4 weeks prior to visit 10, patients must not have missed more than one dose of trial medication and must have self-administered their final dose within 7 days of visit 10. Patients will be reminded by the trial site to self-administer trial medication weekly, to continue this until the completion of visit 10 and to bring their trial medication with them at visit 10 for return. Where more than one dose has been missed during the preceding 4 weeks, visit 10 should be delayed. Self-administration of trial medication should continue at 7-day intervals and then visit 10 rescheduled to ensure no more than one dose of the trial medication has been missed in the previous 4 weeks. Visit 10 should be delayed no more than 14 days if possible, but this can be extended according to local government policy if a patient is unable to attend (for example if a patient is self-isolating) as long as medication use is maintained as above.

- Follow up/ Visit 11

  This should be performed as a telephone visit unless clinical contact is necessary, as per protocol. Where face to face contact is required this should be conducted at the earliest available opportunity.

Study Drug Dispensation and Distribution

If a patient is not able to attend a clinic visit, in order to ensure the continuity of providing patients' study drug within the constraints imposed by the pandemic (or other global crisis), the site staff may decide to supply study drug to patient as follows:

- Adequate supplies of study drug can be shipped to the patient by the study staff using a third-party service with approval from the patient. The third-party vendor will be agreed upon with the sponsor.
- The patient may request, with prior arrangement/agreement with the site, an authorized individual (a relative or delegate) to retrieve the study drug from the study site if the patient is unable to personally to do so.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (e.g., phone calls, emails, video visits) with the sites to get information on study progress, patient

status, and information on issue resolution as detailed in the Data Monitoring Guidelines, Remote source data verification.

If the trial site monitor cannot be on-site to carry out the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be carried out by a pharmacist from the site pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the site pharmacy directly, or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts with Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of patient for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

Clinic visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as the crisis-related limitations permit.

All safety data that are possible to obtain locally should be collected at a remote visit. These measurements may include the use of local practitioners and resources.

Exceptional measures taken in response to a crisis (e.g., COVID-19) and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3 guidance.

8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

Patients will receive lifestyle advice as per routine care from their treating physician.

9. INVESTIGATIONAL PRODUCT

9.1. Dosage and Administration

9.1.1. Randomised Period

During the 24-week randomised treatment period (Figure 1) patients will be randomised in a 1:1 ratio to receive active treatment or placebo.

Either

Presendin (2.0mg exenatide) as a SC injection, self-administered once weekly.

Presendin is supplied as 2 parts, one vial consisting of a drug part (white or grayish white powder in a clear vial) and one pre-filled syringe containing the diluent part (colourless liquid). The drug part is suspended in the diluent part solution and administered as a suspension.

or

Placebo as a SC injection, self-administered once weekly.

Placebo is supplied as 2 parts (visually identical to the Presendin vial and pre-filled diluent syringe). The drug part will exclude the active pharmaceutical ingredient (exenatide acetate) and the diluent part will be the same as the active treatment diluent. The drug part is suspended in the diluent part solution and administered as a suspension.

9.2. Dose Rationale

The proposed 2mg weekly dose was based on the pharmacokinetic performance of the Peptron formulation (PT320). Pharmacokinetic profiles obtained after repeated once weekly dosing of 2mg of PT320 s.c. (as specified in the Presendin IB phase 2 clinical study in patients with type 2 diabetes) were comparable to those predicted by the population PK model developed for weekly s.c. administration of the recommended dose of the 2mg Bydureon extended-release formulation [Cirincione 2017],with time to reach the steady state slightly shorter for PT320 than for Bydureon (7-8 weeks vs 8-10 weeks) and with steady state plasma concentrations remaining within a comparable range for both products. Based on the same molecule and dose, comparable plasma concentrations for PT320 and Bydureon and the established safety profile of Bydureon a similarly acceptable safety and tolerability profile for PT320 is expected.

9.3. Maintaining the Blind

This is a double-blind trial.

A computer/website system will be used to maintain the blind for this trial. The site will be provided with website login details for the system. In the event that the Investigator needs to unblind a patient's treatment, due to a medical emergency, the website should be accessed to unblind for that patient. If possible, the Investigator should discuss this with the IAC and Sponsor prior to unblinding.

9.4. Treatment Assignment

Patients will be randomised in a ratio of 1:1 to receive active treatment (Presendin) or placebo. A computer/website system will be used to randomly assign each patient to a treatment arm.

9.5. Packaging and Labelling

Individual supplies of trial medication will be provided to the sites in a double-blind format. The labels will contain all information required to meet the applicable local regulatory requirements.

Further information on packaging, labelling and dispensing are included in the Pharmacy Manual.

9.6. Preparation

Each dose of trial medication is provided as two parts, a single use vial and a pre-filled syringe of diluent. Patients will receive training and be provided with an instruction sheet with details, on how to store, prepare, self-administer and discard/keep used trial medication.

9.7. Handling and Storage

Presendin, the active trial medication, contains the active ingredient, exenatide, which is hygroscopic and light sensitive and must be protected from light during storage. Prior to use, all trial medication should be stored refrigerated at 2-8ºC.

9.8. Product Accountability and Assessment of Compliance

In accordance with International Council of Harmonisation – Good Clinical Practice (ICH-GCP), each trial centre will account for all supplies of trial medication. Details of receipt, storage, assembly, and return will be recorded. The unit of accountability will be one single active or placebo vial. Both the pre-filled syringe and needle will be disposed of in a sharps box.

All unused supplies will either be destroyed or returned to the trial Sponsor at the end of the trial in accordance with instruction by the Sponsor.

All trial medication will be self-administered by the patients. If a dose is not administered as planned, patients will record the missed dose in their electronic/paper diaries and it will be documented in the electronic case report form (eCRF).

9.9. Treatment of Investigational Product Overdose

In the event a patient overdoses on trial medication the Investigator should be notified as soon as possible. If symptoms appear, the Investigator will treat the patient according to their clinical judgement depending on the type of clinical signs and symptoms exhibited by the patient.

Effects of overdose that may be seen include severe nausea, severe vomiting and rapidly declining blood glucose concentrations.

If a patient receives an overdose of the trial medication, the Sponsor should be notified in writing within 24 hours of the Investigator becoming aware.

9.10. Occupational Safety

There are no known occupational safety risks to staff. The Material Safety Data Sheet will be made available where required by local regulations.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

10.1. Recording Prior and Concomitant Medication

All relevant medication taken within 4 months of screening should be recorded in the eCRF along with all relevant medication taken from the start of the screening period until the final follow-up visit (Section 6.2.1.3).

At a minimum the following information will be collected:

- Generic name
- Dose
- Frequency
- Date started
- If ongoing (or if not, then the date stopped will be recorded)
- Reason for taking the medication

10.1.1. Treatment Failure

Rescue therapy can be initiated when there is a treatment failure.

- Possible treatment failure is defined as those with baseline PMD between -2 and -3.5dB who experience a decline of > or equal to 2dB. In those with a baseline PMD between -3.5 and -7 dB those who experience a decline of > or equal to 3 dB.

When possible treatment failure is identified, perimetry should be repeated.

- Treatment failure is defined as those with baseline PMD between -2 and -3.5dB experience a decline of > or equal to 2dB which remains after repeat perimetry. Or in

those with a baseline PMD between -3.5 and -7 dB who experience a decline of > or equal to 3 dB which remains after repeat perimetry.

These cases should be reviewed urgently by the IAC (who will review all visual and ancillary measures) to confirm or refute a treatment failure

10.1.2. Rescue Therapy/Rescue Intervention for Progressive Visual Loss

When a treatment failure occurs, rescue therapy can be initiated based on the medical judgement of the trial Investigator. Decisions should always be discussed with the IAC as soon as possible and if possible before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to be a medical emergency. In all cases the final decision lies with the trial Investigator.

Patients showing progressive visual loss will be considered for rescue therapy with acetazolamide or an alternative diuretic. In cases where the visual loss is severe and "rapid", and believed by the Investigator to necessitate surgical intervention, the intervention will be conducted in accordance with local emergency practice.

10.1.2.1. Rescue Therapy for Headache

If the Investigator wishes to alter the headache preventative medication (any drug can be considered), this decision should always be discussed with the IAC before any action is taken, unless in the opinion of the Investigator there is no time to do so as it is judged to be a medical emergency. Addition or changing a headache preventive therapy will be considered a protocol deviation. Use of headache preventative medication will be recorded at trial visits.

Use of acute headache analgesics is not considered as rescue medication and is permitted but must be documented in the headache diary (monthly analgesic use).

10.2. Prohibited Medications

10.2.1. Prior to enrolment

- Treatment to lower ICP within 1 week prior to screening (e.g., Acetazolamide, topiramate, diuretics and oral or IV glucocorticoids (including oral dexamethasone and oral prednisolone, excluding inhaled and topical formulations)
- Exposure to fluoroquinolones, lithium, vitamin A, or tetracyclines within 2 months of diagnostic LP
- Botulism toxin or monoclonal antibodies against CGRP or CGRP antagonist injections within previous 4 months

- Greater occipital nerve block within the last 4 weeks
- Glucagon like peptide-1 receptor agonist within last 4 weeks

10.2.2. Prior to randomisation (visit 2)

- Greater occipital nerve block
- Recreational (including cannabidiol) or illicit drugs (including marijuana)

10.2.3. During the trial

- Acetazolamide, topiramate, diuretics and oral or IV glucocorticoids (including oral dexamethasone and oral prednisolone, excluding inhaled and topical formulations). These will be considered rescue medication (Section 10.1.2) and the IAC consulted. This will be considered a protocol deviation.
- If the Investigator alters the headache preventative medication (oral or Botulism toxin or monoclonal antibodies against CGRP or CGRP antagonist injections) this will be considered rescue medication (Section 10.1.2) and the IAC consulted. This will be considered a protocol deviation.
- Greater occipital nerve block
- Glucagon like peptide-1 receptor agonists
- Recreational (including cannabidiol) or illicit drugs (including marijuana)Glucose-lowering medication
- Prescribed weight loss medication
- Regarding COVID-19 vaccination, the risks of receiving or not receiving the vaccination have been considered in relation to the IMP and no additional risks are envisaged. Hence patients may choose to have or not have COVID-19 vaccination or booster during this trial.

11. PATIENT COMPLETION AND WITHDRAWAL

11.1. Patient Completion

Patients will be classed as having completed the trial once they have completed all required trial visits. See Section 10.2.1 for early discontinuations.

11.2. Patient Withdrawal

11.2.1. Patient Withdrawal from Trial Treatment

A patient will be withdrawn from treatment for any of the following reasons:

- Withdrawal of consent to continue in the trial. The reason for this will be documented if provided
- The Investigator or Sponsor, for any reason, decides the patient should be withdrawn from the treatment
- Lack of compliance with the trial medication is classified as <75% or >125% of scheduled doses over the course of the trial, excluding supply issues
- Adverse events, which cannot be tolerated by the patient
- Pregnancy during the treatment period

Patients will be encouraged to continue in the trial to the end of the randomised treatment period even if they stop trial medication so that data can be collected for the Intention-To-Treat (ITT) population.

If a patient is withdrawn from treatment during the randomised treatment period they will be encouraged to return for all trial visits up to visit 10. If a patient does not want to return then at a minimum they should be encouraged to attend for visit 11 procedures as a safety follow-up visit.

11.3. Treatment after the End of the Trial

Patients will not be provided with trial medication following the end of the trial.

11.4. Screen and Baseline Failures

Information will be collected on all patients who sign the Informed Consent Form (ICF).

12. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease

temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

12.1.1. Causal Relationship

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

- Probable relationship: event occurs in a plausible time relationship to the medication administration and cannot be explained by concurrent disease or other drugs or chemicals; the response to the withdrawal of the drug should be clinically plausible
- Possible relationship: event occurs with a reasonable time sequence to the medication administration, but could also be explained by concurrent disease or other drugs or chemicals; information on the drug withdrawal may be lacking or unclear
- Unlikely relationship: event occurs with little temporal relationship to the medication administration and other factors such as drugs, chemicals or underlying disease provide plausible explanations
- Not related: event has no temporal relationship to the medication administration or there is a definite alternative aetiology

12.1.2. Severity Criteria

An assessment of severity grade will be made using the following categorical descriptors:

- Grade 1 means a relatively minor side effect
- Grade 2 means a moderate side-effect
- Grade 3 means a severe or medically significant but not immediately life-threatening side-effect
- Grade 4 means life-threatening consequences
- Grade 5 death related to AE

The exact definition of each number in the scale depends on the particular side effect according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [CTCAE].

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the patient (e.g., laboratory abnormalities).

Adverse events occurring as a result of LP should be specifically recorded. Occurrence of post lumbar headache will be specifically reported.

12.1.3. Reporting Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the patient's last trial-related procedure (which may include contact for follow-up of safety). The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol. Adverse events reported after dosing will be classed as treatment emergent AEs.

All AEs, regardless of seriousness, severity, or presumed relationship to trial therapy, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common aetiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the source documents and the eCRF their opinion concerning the relationship of the AE to trial therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

The patient must be provided, on the first day of trial medication (Day 1), with a "patient card" indicating the following:

- Patient number
- Name of the investigational product
- Investigator's name and 24-hour contact information
- Statement that the patient is participating in a clinical trial

12.2. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not reach the above definition but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an accident and emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Deterioration of IIH necessitating CSF shunting or optic nerve sheath fenestration or dural venous sinus stenting will be recorded as an SAE and reported.

Deterioration of IIH necessitating hospital admission will be recorded as an SAE and reported.

Pre-defined exclusions:

- Hospitalisation for unrelated elective procedures
- Post LP headache

12.2.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to the trial medication and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator Brochure) and serious.

12.2.2. Expected Adverse Events

Perceived deterioration of IIH necessitating attendance or admission to hospital will not be reported as an SAE, but these events will be reported and recorded at follow-up. Non-protocol LPs will be reported at follow-up.

12.2.3. Reporting Serious Adverse Events

All SAEs occurring during clinical studies must be reported to the appropriate Sponsor designee (contract research organisation) within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the Sponsor's safety contact using the SAE Form, which must be completed and signed by the Investigator, and transmitted to the Sponsor's safety contact within 24 hours.

The contact details are:

[redacted]

The Sponsor assumes responsibility for appropriate reporting of SAEs or SUSARs to the regulatory authorities. The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee (IEC) that approved the protocol unless otherwise required and documented by the IEC.

An annual safety report will be submitted to the Institutional Review Board once a year via the Investigator.

12.3. Reporting and Handling of Pregnancies

Pregnant patients will be withdrawn from the trial.

Female patients will be instructed to notify the Investigator immediately if they become pregnant during the trial and up to 12 weeks after discontinuation/completion of trial medication. Pregnant patients will be withdrawn from further trial treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the trial.

A pregnancy as such is not an AE, unless there is a possibility that the trial medication has interfered with the efficiency of any contraceptive measures. The Investigator should report all pregnancies to the Sponsor contact or designee within 24 hours of being informed of them. The pregnancy report form should be used instead of the SAE form.

The pregnant patients will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

Patients will give consent on enrolment that the Investigator will report any pregnancy to the Sponsor and that further information will be collected until delivery.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Before patients are enrolled, a Statistical Analysis Plan (SAP) will be finalised providing detailed methods for the analyses outlined below.

13.1. Hypotheses

This trial compares outcomes in IIH patients under Presendin and matched placebo. The primary hypothesis that will be tested is:

- The ICP measurement in the Presendin group is equal to the ICP measurement in the placebo group at Week 24; against the alternative that the outcomes differ

13.2. Trial Design Considerations

13.2.1. Sample Size Assumptions

The target sample size for the trial is 240 randomised patients, i.e., 120 patients per arm. We justify this figure in the following sections. The two outcomes for which we sought to power the study are ICP and MHD. It transpired from the study of previous literature and trials that MHD was subject to relatively more variability and required the greater sample size to achieve nominal power to detect the sought difference. Thus, it was the powering of the test of MHD that determined the sample size for the trial. For that reason, we commence the justification of the sample size below using MHD, even though it is not the primary outcome measure. In a following section, we convey power at this sample size for the test of ICP.

Operating performance at the target sample size for testing differences in MHD was assessed by computer simulation. Vectors for the daily probability of headache during months 0, 1, …, 6 were specified for the placebo and experimental arms, and the logits of these vectors were used as the intercepts in the data-generating models (DGMs). Patient-level susceptibilities were sampled from a $N(0, 0.7^2)$ distribution and fixed throughout the simulated trial, performing the role of patient-level adjustments to the intercept on the log-odds scale in the DGM. Random patient-level gradients were sampled from a $N(0, 0.2^2)$ distribution and used to reflect patient-level trends in the log-odds of headache. Random errors were sampled from a $N(0, 0.7^2)$ distribution, performing the role of independent homoskedastic random errors on the log-odds scale. The probability of headache is the inverse logit of the sum of these terms (with the gradients scaled by time) and the number of headache days was sampled as a binomial random variable between 0 and 28. The parameters in the DGMs were chosen to yield repeated measures outcomes that have similar variability and serial correlation to those observed in previous IIH trials.

Data missingness was incorporated into our simulations using a method we describe as "randomly sampled departures". The method can be visualised using the following table where white cells reflect that a measure was obtained and orange cells reflect that data is missing:

Patient	t0	t1	t2	t3
1				
2				
3				
4				
5				
6				

In this method, patients reliably provided data up until the time that they departed the trial, and then never provided data again. Under such a scheme, later time-points are more likely to be missing than earlier time-points, some patients provide full data, and some patients provide no data, despite being randomised. Each of these features is possible in data we expect to collect in our trial.

The method takes a data set and arrives at a state where $100 \times \omega\%$ of the data is missing by invoking the following iterative algorithm:

1. Randomly sample a patient for which some data will be missing.
2. Randomly sample a time-point from the list of protocol-specified assessment times. This is the patient's departure point.
3. Remove all observations for the patient at or after their departure point.
4. If the percentage of missing data is less than ω, go to step 1

Using this algorithm, we removed 20% of data in the simulations used to infer statistical performance. The 20% value was adjudged to be realistic by the sponsor based on previous trials in IIH.

For each simulated dataset, we then tested the presence of treatment effects using a likelihood ratio test of nested models. Let i index patients and j index time so that y_{ij} represents the measured outcome for the ith patient at the jth protocol-specified assessment time. Let N be the total number of patients and J the total number of assessment times. Furthermore, let z_i be an indicator variable, taking the value 1 when patient i is allocated to the experimental arm or 0 when they are allocated to placebo.

The main analysis model was:

$$y_{ij} = \beta_0 + a_i + b_i t + \beta_1 I(j = 1) + \cdots + \beta_j I(j = J) + \gamma_1 I(j = 1) I(z_i = 1) + \cdots$$

$$+ \gamma_J I(j = J) I(z_i = 1) + \epsilon_{ij}$$

and the alternative model was:

$$y_{ij} = \beta_0 + a_i + b_i t + \beta_1 I(j = 1) + \cdots + \beta_j I(j = J) + \epsilon_{ij}$$

where $\epsilon_{ij} \sim N(0, \sigma^2)$, $a_i \sim N(0, \sigma_a^2)$, $b_i \sim N(0, \sigma_b^2)$ and *I(A)* is the indicator function, taking the value 1 when *A* is true, else taking the value 0. That is, we used a mixed effects model where time is treated as a factor variable for estimating treatment effects, with normally distributed patient-level intercepts, normally distributed patient-level gradients with respect to continuous time, and normally distributed errors.

In this model, the $\beta_j$terms represent the mean changes from baseline in the placebo group. The γ_j terms represent the treatment effects, being the mean difference in outcome between the arms at time *j*. In a scenario where the drug has effects indistinguishable from placebo, $\gamma_1 = \cdots = \gamma_J = 0$

Using this method, we observed by simulation that the type I error rate was controlled at the nominal 5% level when there were no differences in probability of headache between the two arms. Furthermore, we observed that power was approximately 88% when the mean MHD in the experimental arm was (0.0, 2.4, 2.5, 2.6, 2.8, 2.9, 3.0) days lower than placebo in months 0 to 6.

13.2.1.1. Intracranial Pressure Power

Initially, for the purposes of estimating power, we assume that ICP standard deviation is 6.0 cm H_2O CSF in placebo and Presendin treated patients at baseline, 6.0 in placebo patients at 24-weeks, and 7.0 in Presendin treated patients at 24-weeks. By way of justification of these assumptions, we note that baseline standard deviations of ICP in previous trials were: 5.4 (n=10) and 6.3 (n=17) in the Drug Trial [Markey, 2017]; 5.0 (n=16) (data on file); and 5.7 (n=32) and 5.3 (n=30) in the Weight Trial [Ottridge, 2017]. Post-baseline standard deviations were slightly lower (and less than 6.0) in three of these five arms; and increased slightly in one (but remained less than 6.0). The post-baseline standard deviation however increased to over 8.0 in the surgery arm of the Weight Trial, because the surgical intervention dramatically impacted ICP in some patients. Conservatively, we therefore estimate that post-baseline standard deviation will be 6.0 in the control arm. We anticipate that the standard deviation will be slightly higher in the experimental arm as treatment effects will potentially manifest changes in ICP. However,

we do not expect variability to be as inflated in this trial relative to control as it was in the Weight Trial, because of the likely difference in effect between surgical and drug interventions. For this reason, we have predicted in the Presendin arm that post-baseline standard deviation will be 7.0.

Under this parameterisation, when testing for a difference between arms at 24-weeks of 5 cm H_2O CSF using a total sample size of 240, assuming that up to 30% of observations are missing, using a 5% significance level by Analysis of Covariance (ANCOVA) adjusted for baseline ICP, the two stratification variables, and treatment arm, we expect to have approximately 99% power. This has been inferred by computer simulation.

In the NORDIC trial [Wall, 2014], the standard deviation of baseline ICP was higher, at 9.4 cm H_20 in the treatment arm (n=86). To stress-test the power analysis presented above, we investigated the following values: control arm baseline and 24-week ICP SD equals 9.4, Presendin baseline ICP SD equals 9.4, and Presendin 24-week ICP SD equals 10.4. These values assume the variability of ICP measures in untreated patients is as high as has been seen in an IIH trial, and assumes that the variability in treated patients is slightly higher still. Mimicking the above method with these revised values, when testing for a difference between arms at 24-weeks of 5 cm H_2O CSF using a total sample size of 240, assuming that 30% of observations are missing, using a 5% significance level by Analysis of Covariance (ANCOVA) adjusted for baseline ICP, the two stratification variables, and treatment arm, we expect to have at least 90% power.

Outcomes from previous trials show that baseline and post-baseline distributions of ICP show central tendency with approximate symmetry, so we conclude that normality is a reasonable assumption and therefore ANCOVA is a defensible analysis method.

13.2.1.1. Perimetric Mean Deviation Power

We convey here estimated power for detecting differences between arms in the PMD outcome measure. In the NORDIC trial [Wall, 2014], the authors observed that the decrease from baseline to 6-months in PMD was 0.71dB greater in the experimental arm than the control arm. Cross-sectional SD of PMD was 1.1-1.2 at baseline. Table 2 in their publication shows that the standard error of mean PMD is higher at 6m than at baseline, likely reflecting a combined effect of missing data at 6m and greater variability of post-baseline measures. We plan to take repeated measures of PMD at baseline, 2m, 4m and 6m. Assuming that the overall SD of PMD scores is 1.5, thus introducing some inflation on Wall *et al.*'s baseline for the reasons identified, using the formula given on p.31 of Diggle, Liang & Zeger (1994), we would expect to require 138 patients in total to detect a difference of 0.71dB with 90% power at a 5% significance level, if the serial correlation between repeated measures is 0.5 (we expect a value in this region) [Diggle, 1994]. If the serial correlation parameter is as low as 0.3, the required sample size increases to 192. Note that these methods assume full follow-up and data collection. Naturally, some

missing data is expected but we expect the aggregate data from the n=240 group to make up any shortfall. This section assumes a longitudinal analysis method like hierarchical regression.

13.2.2. Stratification

At the outset, it is expected that duration of symptoms attributed to IIH will be prognostic of potential efficacy. For this reason, it is proposed to stratify randomisation by duration of diagnosis (≥ 2 weeks from diagnostic LP), previous diagnosis of migraine, baseline ICP (≥35 cm), baseline Body mass index (≥30 kg/m^2).

13.2.3. Sample Size Sensitivity

13.2.3.1. Clinically Meaningful Effect Sizes

Minimally relevant effect sizes have not been fully determined in IIH given it is a rare disease with relatively few previous trials.

The ICP diagnostic threshold in IIH is 25 cm H_2O [Mollan, 2018]. However, it is not necessary to reduce ICP <25 cm H_2O to achieve remission from signs and symptoms of IIH in all patients [Sinclair, 2010]. The clinical importance of a particular change in ICP will vary depending on the starting ICP and the impact this pressure has on vision and headache. Changes in ICP of 5 cm H_2O are generally considered meaningful when treating IIH patients. For example, in a clinical study evaluating the benefits of weight loss in IIH patients, a 16.5% (6.2 cm H_2O) reduction in ICP resulted in a statistically significant improvement in headache and vision measures as well as quality of life [Sinclair, 2010]. In the IIH Treatment trail (n=165), a study evaluating the drug treatment acetazolamide against placebo, a reduction of -5.9 cm H_2O was seen in association with significant improvement in PMD, OCT measures of papilloedema and quality of life measures [Wall, 2014].

The minimally clinically important change in the perimetric mean deviation adopted into clinical practice was stablished by the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) group and the IIH Treatment Trial (IIHTT). The investigators found a 0.71dB difference in the PMD between the two trial arms (comparing acetazolamide with placebo) that was clinically meaningful. The change of 0.71dB was interpreted as clinically meaningful as this was in the setting of significant changes in LP opening pressure, papilloedema (measured by OCT), general quality of life and visual related quality of life [Wall, 2014, Bruce, 2016].

The clinically meaningful effect size for MHD reflects that for a phenotypically similar headache, chronic migraine. Recent randomised trials in patients with chronic migraine [Tepper, 2017; Silberstein, 2017], episodic migraine [Goadsby, 2017], or both

[Camporeale, 2018] have shown in post-baseline months 1–3, odds of migraine relative to baseline of 0.5–0.8 with placebo and 0.5–0.3 with experimental drugs. Decreases in MHD relative to baseline grew in time, and placebo responses were stronger in chronic migraine than episodic migraine. In the three placebo-controlled, blinded trials, these equated to odds-ratios of migraine compared with placebo of 0.8–0.6, or absolute differences of 1.5–2.5 MHD [Sinclair, 2010; Tepper 2017; Silberstein, 2017; Goadsby, 2017].

13.2.4. Sample Size Re-estimation

No sample size re-estimation of the overall sample size will be performed.

13.2.5. Trial Stopping Criteria

There are no trial-specific stopping rules.

13.3. Data Analysis Considerations

13.3.1. Estimands

We have specified intercurrent events that are material to the measurement of our primary and secondary outcomes, and unbiased estimation of treatment effects attributable to Presendin.

ICP-lowering medication include: acetazolamide, topiramate, diuretics, glucocorticoids (oral dexamethasone and oral prednisolone). Headache-preventative medications include: amitriptyline, topiramate, nortriptyline, beta blockers, candesartan, sodium valproate, pizotifen, botox, CGRP-therapy.

13.3.1.1. Outcome: Intracranial pressure (ICP)

13.3.1.1.1. Intercurrent event: ICP-lowering medications

All patients are expected to have elevated ICP because it is a defining characteristic of the disease. ICP is a physiological variable that is unlikely to show spontaneous improvement without treatment. For these reasons, we expect ICP-lowering medication use to be greater in the placebo arm. If a patient takes medication that is intended to reduce their ICP, it is logical to expect that their ICP will be reduced. Outcomes from patients that take ICP-lowering medications will confound the estimation of the causal treatment effect of Presendin. We have no data to estimate the length of effects of ICP-lowering medications. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have used ICP-lowering medications and replace these observations with arm-specific imputations. This will allow estimation of the treatment effect that is

purely and causally attributable to Presendin. Patients will consent at enrolment to forgo the use of ICP-lowering medications, and be informed that taking ICP-lowering medications during the trial would constitute rescue therapy and be a protocol deviation.

13.3.1.1.2. Intercurrent event: Off-protocol lumbar punctures

Lumbar punctures are commonly conducted to reduce intracranial pressure [Weisberg, 1977; Johnston, 1981; De Simone, 2005]. In some centres, they are given routinely although this has now been advised against in the International IIH Guidelines (Soler, 1998; Mollan, 2018). As such, they remain a material therapeutic option. LP is expected to reduce ICP mean opening pressure 32 (28-37) cm CSF to 19 (17-21) cm CSF post LP [Yiangou, 2019]. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify change in ICP after an LP, it is expected that effects in the majority of change would have dissipated completely within two months [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that have had an off-protocol LP within two months of the protocol-scheduled 24-week LP, and replace these observations with arm-specific imputations. Where patients require off-protocol LP this would be a protocol deviation.

13.3.1.1.3. Inter-current event: Dramatic weight-loss following surgery

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in ICP [Sinclair, 2010]. We do not regard gradual weight-loss arising from changes to diet, lifestyle or exercise to be intercurrent events. However, sudden dramatic weight loss arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove 24-week ICP outcomes from all patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure and replace with arm-specific imputations. Patients will be ineligible for the trial if they have had a surgical weight-loss procedure within 3 months of randomisation or fail to confirm that they do not intend to undertake such a procedure during the trial. They will also be informed at enrolment that undergoing a surgical weight-loss procedure would be a protocol deviation.

13.3.1.2. Outcome: Perimetric Mean Deviation (PMD)

13.3.1.2.1. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease

and that papilledema will reduce as a result, allowing visual fields to improve. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the PMD outcomes following the administration of ICP-lowering medications, and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.2.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilledema, allowing visual fields to improve. Patients that have LPs are expected to experience less pressure on the optic nerve, less papilledema, and have better chances of visual fields improving. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilledema after an LP the consensus of clinicians would predict that effects of the LP on papilledema and therefore visual fields would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. PMD outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove PMD outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.2.3. Intercurrent event: Dramatic weight-loss following surgery

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including improvements in visual fields [Sinclair, 2010]. We do not regard gradual weight-loss arising from changes to diet, lifestyle or exercise to be intercurrent events. However, sudden dramatic weight loss arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove PMD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.3. Outcome: Papilledema measured by OCT (including central thickness, CT, retinal nerve fibre layer, RNFL)

13.3.1.3.1. Intercurrent event: ICP-lowering medications

All patients will suffer from papilledema at enrolment and it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that the papilledema will reduce in turn. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the OCT outcomes following the administration of ICP-lowering medications, and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.3.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilledema. Patients that have LPs are expected to experience less pressure on the optic nerve and therefore relatively less papilledema. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilledema after an LP the consensus of clinicians would predict that effects of the LP on papilledema would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. OCT outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove OCT outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.3.3. Intercurrent event: Dramatic weight-loss following surgery

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in papilledema [Sinclair, 2010]. We do not regard gradual weight-loss arising from changes to diet, lifestyle or exercise to be intercurrent events. However, sudden dramatic weight loss arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove OCT outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with

patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4. Outcome: Monthly headache days (MHD)

13.3.1.4.1. Intercurrent event: Headache-preventative medications

The great majority of patients are expected to suffer from headache because it is a common symptom of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes medication that is intended to prevent headache, it is logical to expect that their headache burden will be decreased. Despite the widely-observed short-term placebo-effect observed in headache outcomes, we expect headache-preventative medication use to be greater in the placebo arm. Outcomes from patients that take headache-preventative medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the headache outcomes following the administration of headache-preventative medications, and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin. Patients will consent at enrolment to forgo the use of Headache-preventative medications, and be informed that taking such medicines during the trial would be regarded as rescue therapy and be a protocol deviation.

13.3.1.4.2. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing the frequency and intensity of headache. Beneficial effects dissipate with time. Prospective data documents alterations in headache for at least 7 days and whilst there is no prospective longitudinal data over a longer time period consensus amongst clinicians would widely acknowledge that headache in some individuals can be influenced for up to a month [Yiangou, 2019]. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. MHD outcomes will be recorded daily via diaries. For the reasons stated, we propose to remove MHD outcomes recorded in the 4-weeks following each off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.3. Intercurrent event: Dramatic weight-loss following surgery

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including decreases in headache frequency and severity [Sinclair, 2010]. We do not regard gradual weight-loss arising from changes to diet, lifestyle or exercise to be

intercurrent events. However, sudden dramatic weight loss arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove MHD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.4. Intercurrent event: ICP-lowering medications

All patients are expected to suffer from some visual field loss at enrolment because it is the hallmark feature of the disease [Wall, 2014; Ottridge, 2017; Markey, 2020]. If a patient takes ICP-lowering medication, it is logical to expect that their ICP will decrease and that papilledema will reduce as a result, allowing visual fields to improve. As stated, we expect ICP-lowering medication use to be greater in the placebo arm. Outcomes from patients that take these medications will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove the PMD outcomes following the administration of ICP-lowering medications, and replace these observations with imputations generated by a method suitable for longitudinal data imputation. This will allow estimation of the treatment effect that is purely and causally attributable to Presendin.

13.3.1.4.5. Intercurrent event: Off-protocol lumbar punctures

As discussed above, LPs are a material and widespread intervention in the treatment of IIH, given with the intention of reducing intracranial pressure and improving the associated symptoms of the disease, including reducing pressure on the optic nerve and papilledema, allowing visual fields to improve. Patients that have LPs are expected to experience less pressure on the optic nerve, less papilledema, and have better chances of visual fields improving. Beneficial effects dissipate with time and whilst there has been no longitudinal assessment to quantify papilledema after an LP the consensus of clinicians would predict that effects of the LP on papilledema and therefore visual fields would have dissipated by one month. Outcomes from patients that have undergone off-protocol LPs will confound the estimation of the causal treatment effect of Presendin. PMD outcomes will be recorded repeatedly during the trial. For the reasons stated, we propose to remove PMD outcomes recorded in the 4-weeks following an off-protocol LP, and replace these observations with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.4.6. Intercurrent event: Dramatic weight-loss following surgery

Research has shown that weight loss in IIH is associated with reductions in IIH symptoms, including improvements in visual fields [Sinclair, 2010]. We do not regard

gradual weight-loss arising from changes to diet, lifestyle or exercise to be intercurrent events. However, sudden dramatic weight loss arising from a surgical procedure will likely yield material changes to IIH symptoms. This will confound the estimation of the causal treatment effect of Presendin. For these reasons, we propose to remove PMD outcomes of patients that experience weight loss exceeding 10% of baseline weight after a surgical weight-loss procedure from the date of procedure. These outcomes will be replaced with patient-within-arm imputations generated by a method suitable for longitudinal data imputation.

13.3.1.5. Primary Estimand (Hypothetical assuming no concurrent procedures, irrespective of adherence to treatment)

The primary estimand is defined as the following for the primary endpoint:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect ICP.

The primary estimand for the initial secondary endpoint will be handled similarly to the primary endpoint using the "Hypothetical" approach. The initial secondary endpoint is defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, regardless of adherence to randomised treatment, where patients did not have medications or procedures likely to materially affect PMD.

13.3.1.6. Secondary Estimand (Hypothetical)

The secondary estimand for the primary endpoint is defined as follows:

- Treatment difference in ICP measurement between Presendin and placebo at Week 24 for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect ICP.

The secondary estimand for the initial secondary endpoint will be defined as:

- Treatment difference in PMD between Presendin and placebo over 24-weeks for all patients who are randomised and start treatment, if all patients adhered to treatment, where patients did not have medications or procedures likely to materially affect PMD.

All details will be defined in the SAP.

13.3.2. Analysis Populations

The following analysis populations are planned for this trial:

- **Safety Population:** The Safety population includes all patients randomised to treatment who receive at least one dose of trial medication. This will be the population used for all safety analyses unless otherwise specified.
- **Intent-To-Treat Population (ITT):** The ITT population includes all patients randomised to treatment. This will be the main population for all efficacy analyses unless otherwise specified.
- **Per Protocol (PP)**: The PP population includes all patients randomised to treatment who complete the trial without important non-evaluable protocol deviations. Only protocol deviations with the potential to affect the trial results significantly, or to invalidate the interpretation of the data obtained, will lead to exclusion of patients from the PP population. Protocol deviations to be considered will include (but will not be limited to):
    - Failure to meet inclusion/exclusion criteria
    - Wrong treatment or incorrect volume of drug administration
    - Prohibited concomitant medications
    - Compliance of less than 75% and >125% with trial drug administration
    - Use of rescue procedures, including, off-protocol LPs, LP shunts or bariatric surgery

Assignment of patients to populations will be confirmed at a blinded data review meeting to be held before the trial database is locked.

If a patient is randomised incorrectly or is administered the incorrect trial medication, analyses of the ITT will be based on the assigned treatment, whereas all other analyses will be based on the actual treatment received.

13.3.3. Treatment Comparisons

Treatment comparisons will be undertaken between active and control groups.

13.3.4. Safety Analyses

Safety will be evaluated from reported AEs, changes in clinical laboratory values, changes in vital signs, and ECG results.

All safety analyses will be performed on the Safety population.

13.3.4.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary (the most recent version before starting the trial will be used).

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

Guidance for programmers on how to handle missing fields relating to AEs will be given in the SAP.

The number and percentage of patients reporting TEAEs, grouped by MedDRA system organ class and preferred term will be tabulated by treatment group and observation period. Summaries will be presented for all TEAEs, TEAEs by severity and TEAEs by relationship to trial medication.

In the case of multiple occurrences of the same TEAE within the same patient, each patient will only be counted once for each preferred term. If a patient experiences' more than one TEAE within a preferred term, only the TEAE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.

In the summaries showing severity and relationship to trial medication, the event with the maximum severity or strongest relationship will be reported. 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).

Adverse event table summaries will be split by observation period. Adverse events with a start date after first dose of trial drug and up to and including date of Week 24 assessment will be presented in the randomised treatment period.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged. The observation period in which an AE started will also be provided.

Non-protocol LPs, interventions for IIH, hospital admission for IIH exacerbation will be displayed. Treatment failures will be displayed by trial arm.

13.3.4.2. Clinical Laboratory Evaluations

Laboratory test results for each biochemistry and haematology parameter will be summarized descriptively by treatment group and time point as both observed values and change from baseline values.

The number of patients with clinical laboratory (biochemistry, haematology, and urinalysis) values categorized as below, within, or above the normal ranges (or as either normal or abnormal for urinalysis variables that do not have quantitative ranges), will be tabulated in relation to baseline (shift tables), for each clinical laboratory analyte by treatment group and time point.

Laboratory values will be displayed in the data listings and those that are outside the reference ranges will be flagged, along with corresponding normal ranges. Any patients with any markedly abnormal laboratory results will also be provided in a listing.

All laboratory summaries will be prepared for the period of randomised treatment.

Pregnancy test results including reason, if not performed, will be listed.

13.3.4.3. Vital Signs and Body Mass Index Evaluations

Descriptive summaries of observed values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure and heart rate by treatment group and time point.

Body mass index will be derived at Screening, Baseline and Weeks 4, 8, 16, 24, 32 and 48 using height captured at Screening and weight at the respective assessment. Body mass index and weight will be summarized descriptively by treatment group and time point as both observed values and change from baseline values for Safety and ITT populations.

Summaries will be prepared for the period of randomised treatment.

13.3.4.4. Electrocardiogram

Descriptive statistics of observed values and change from baseline will be presented for ECG measures of PR interval, QRS interval, QT interval, QT interval corrected according to Fridericia's formula (QTcF). These summaries will be presented by treatment and time point for the Safety population.

The number and percentage of patients with values beyond clinically important limits will be summarised including those with an increase in QTcF >30 msec increase from

baseline and >60 msec increase from baseline or those with an absolute QTcF value of >450 msec (male patients) or >470 msec (female patients).

Summaries will be prepared for the period of randomised treatment.

13.3.5. Patient Reported Outcomes Analyses

All patient reported outcome endpoints (VFQ-25, HIT-6, SF-36, EQ-5D-5L) will be analysed as observed and presented with change from baseline in a descriptive summary of treatment and visit for the period of randomised treatment.

The number and percentages of PGIC responses will be tabulated by treatment and visit.

13.3.6. Missing Data

Although every effort will be made to collect responses from all patients at all scheduled time points, there undoubtedly will be some missing data. The SAP will describe detailed steps for dealing with missing data using an iterative regression based multiple imputation strategy that adjusts for treatment arm, centre, baseline value, and stratification variables.

13.3.7. Reporting Deviations from the Statistical Plan

Any deviations from the planned analyses will be described and justified in the final clinical trial report.

14. TRIAL ADMINISTRATION

14.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Before initiation of a trial site, the Sponsor will obtain approval from the appropriate regulatory agency to conduct the trial in accordance with ICH-GCP and applicable country-specific regulatory requirements.

The trial will be conducted in accordance with all applicable regulatory requirements.

The trial will be conducted in accordance with ICH-GCP, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2013, including, but not limited to:

- An IEC/Institutional Review Board review and approval of trial protocol and any subsequent amendments and all ICFs or other information given to the patient

- Patient informed consent
- Investigator reporting requirements

The Sponsor will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each patient before participation in the trial. Written informed consent will be collected following a review of the patient's information leaflet by the potential patient and a discussion between the patient and the Investigator or suitably qualified designee.

The Investigator will cooperate with all regulatory inspections and will notify the Sponsor as soon as they are aware of an inspection which may involve this trial. With the exception of statutory regulatory authority inspections, the Sponsor will be consulted in the event of inspection of the clinical site(s) by an outside authority before the Inspectors are permitted access to any of the trial records or the trial areas.

14.2. Trial Monitoring

In accordance with applicable regulations, ICH-GCP, the monitoring plan and the Sponsor's and/or delegate procedures, monitors will contact the site before the start of the trial to review with the site staff the protocol, trial requirements, and their responsibilities to satisfy regulatory, ethical, and the Sponsor's requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The Sponsor and or delegated monitors will perform risk-based monitoring during the conduct of the trial to ensure that:

- The data are authentic, accurate and complete
- The patient's safety and rights are being protected
- The trial is conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP and all applicable regulatory requirements

14.2.1. Access to Source Data

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor, Sponsor-appointed auditors and regulatory inspectors direct access to all relevant documents.

14.2.2. Data Handling and Record Keeping

Following closure of the trial, the Investigator or head of the medical institution (where applicable) must maintain all site trial records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Sponsor audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

The Sponsor will inform the Investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, the Sponsor SOPs and/or institutional requirements.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the Investigator is no longer associated with the site.

14.3. Provision of Trial Results and Information to Investigators and Publications

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical trial report. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review the complete trial results at a mutually agreeable location.

The Sponsor will also provide the Investigator with the full summary of the trial results. The Investigator is encouraged to share the summary results with the trial patients, as appropriate.

If the Sponsor decides to publish the results, then they will provide the Investigator with an opportunity to review the manuscript. If the Investigator wishes to publish anything related to the trial, then they must provide the Sponsor with the draft publication and

allow them no less than 14 days to review the document. The Investigator cannot publish without written authorisation from the Sponsor.

14.4. Data Management

For this trial, patient data will be collected using an eCRF and combined with data provided from other sources in a validated data system. Patient's identifiable data (e.g., name, initials, address etc.) will not be collected in the eCRF or transferred to Invex Therapeutics. Clinical data management will be performed with the objective of removing errors and inconsistencies in the data which would otherwise impact on the statistical analysis or the credibility of the Clinical Study Report. Original CRFs will be retained by Invex Therapeutics; the Investigator will also retain a copy.

Management of clinical data will be performed in accordance with the applicable Sponsor standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Affairs and World Health Organisation Drug dictionary.

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor or designee will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation)
b. Maintain SOPs for using these systems
c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail)
d. Maintain a security system that prevents unauthorised access to the data
e. Maintain a list of the individuals who are authorised to make data changes
f. Maintain adequate backup of the data
g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing)

Training on the use of the electronic data collection system will be provided to all relevant trial site staff.

14.5. Independent Adjudication Committee

The IAC will consist of three international medical experts in neurology or ophthalmology who are independent of the Sponsor team and Investigators running the trial.

The role of the IAC will be:

- To support the Investigators with opinions on the eligibility of potential patients
- To provide opinions regarding rescue medications required during the trial

Further details on the composition, activities and responsibilities of the IAC can be found in the IAC charter.

14.6. Data Safety Monitoring Committee

Details on the composition, activities and responsibilities of the DSMC can be found in the DSMC charter.

14.7. Insurance, Indemnity and Finance

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

The Sponsor will indemnify all Investigators participating in this trial against future claims by trial patients; the terms of this will be detailed within a separate letter of indemnification. The indemnity will only apply where all trial procedures have been carried out according to this protocol.

The financial aspects of the trial are addressed in a separate agreement.

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16. APPENDICES PROVIDED FOR TRIAL INVEX-CLIN-IIH-301

16.1. Appendix 1: IIH Diagnostic criteria [Mollan, 2018]

A. Papilloedema

B. Normal neurological examination (except sixth cranial nerve palsy)

C. Neuroimaging: normal brain parenchyma (no hydrocephalus, mass, structural lesion or meningeal enhancement). Venous thrombosis excluded in all.

D. Normal CSF constituents (less than or equal to 7 white cells per mm^3 with normal protein and glucose

E. Elevated lumbar puncture pressure ≥ 25cmCSF

16.2. Appendix 2: 36-item short from survey

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

○ 1 - All of the time

○ 2 - Most of the time

○ 3 - Some of the time

○ 4 - A little of the time

○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

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16.3. Appendix 3: EuroQol -5 dimension-5 level survey

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

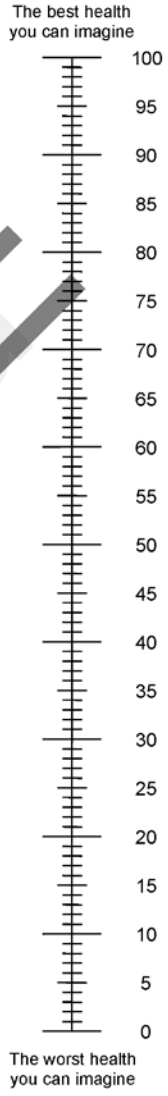
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

16.4. Appendix 4: Headache Impact Test-6

HIT-6™
(VERSION 1.1)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1 When you have headaches, how often is the pain severe?

Never | Rarely | Sometimes | Very Often | Always

2 How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never | Rarely | Sometimes | Very Often | Always

3 When you have a headache, how often do you wish you could lie down?

Never | Rarely | Sometimes | Very Often | Always

4 In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never | Rarely | Sometimes | Very Often | Always

5 In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never | Rarely | Sometimes | Very Often | Always

6 In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never | Rarely | Sometimes | Very Often | Always

SAMPLE

COLUMN 1 (6 points each) + COLUMN 2 (8 points each) + COLUMN 3 (10 points each) + COLUMN 4 (11 points each) + COLUMN 5 (13 points each)

To score, add points for answers in each column.
Please share your HIT-6 results with your doctor.

Total Score

Higher scores indicate greater impact on your life.

Score range is 36-78.

HIT-6™ US (English) Version 1.1
©2000, 2001 QualityMetric, Inc. and GlaxoSmithKline Group of Companies

HEADACHE IMPACT TEST™

What Does Your Score Mean?

If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your doctor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

About HIT

The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36®' health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

SF-36® is a registered trademark of Medical Outcomes Trust and John E. Ware, Jr.

16.5. Appendix 5: Visual Function Questionnaire-25 & 10-item Supplement

PB/SA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accessing and using this document:

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7/29/96

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don't apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

(Circle One)

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

- No difficulty at all 1
- A little difficulty 2
- Moderate difficulty 3
- Extreme difficulty 4
- Stopped doing this because of your eyesight 5
- Stopped doing this for other reasons or not interested in doing this 6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

12. **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. **Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?**

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. **Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?**

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. **Are you currently driving, at least once in a while?**

(Circle One)

Yes..... 1 *Skip To Q 15c*

No 2

15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Never drove..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight..... 1 *Skip To Part 3, Q 17*

Mainly other reasons..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty 3
Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DRIVING

A10. [This item, "driving in difficult conditions", has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?.....	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?.	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

10-ITEM NEURO-OPHTHALMIC SUPPLEMENT TO THE NEI-VFQ-25

The following are additional questions and statements about problems that involve your vision or feelings you may have about your vision condition. After each question, there will be a list of possible answers. Please choose the response that best describes your situation.

Please answer all questions as if you were wearing your glasses or contact lenses (if any). Please take as much time as you need to answer each question.

1. How much difficulty do you have performing tasks when your eyes are tired?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

2. Because of your vision, how much difficulty do you have identifying objects or performing tasks in bright sunlight?
(Circle One)

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

3. Because of your vision, how much difficulty do you have parking a car?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

4. Because of your vision, how much difficulty do you have using a computer?
(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

For each of the following statements, please indicate if it is definitely true, mostly true, mostly false, or definitely false for you or if you are not sure.

5. I have a feeling that my two eyes see differently, even with correction (glasses or contact lenses).
(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

6. I have a feeling that my eye or eyelid appearance is unusual.
(Circle One)

Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

For each of the following, please indicate if it is true for you all, most, some, a little, or none of the time.

7. My vision is blurry, not clear, or "fuzzy."
(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

8. I have trouble focusing on or following moving objects.
(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

9. I have double vision with both eyes open that is not present when either eye is covered.
(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

10. My eyelid(s) droop.
(Circle One)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

16.6. Appendix 6: Patient Global Impression of Change

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is

✓*one box only:*

[1] ☐ Very much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very much Worse

16.7. Appendix 7: Contraception

Birth control methods which may be considered as highly effective (that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods).

Patients should be instructed not to take their oral contraceptive within 1 hour prior to administration of trial medication.

Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [1]
- sexual abstinence [2]

[1.] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant.

[2.] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.