ASX Announcement
20 May 2020

Exenatide Meets Key Endpoints in IIH Clinical Trial

- **Statistically significant reduction in Intracranial Pressure (ICP, the Primary Endpoint) shown in Idiopathic Intracranial Hypertension (IIH) patients receiving Exenatide at 2.5 hrs, 24 hrs and 12 weeks (range 18.1-20.8% versus study hurdle of >10%)**
- **First ever human study to demonstrate ICP lowering effects of Exenatide in IIH patients**
- **Statistically significant & clinically meaningful 7.7 day (37%) reduction in Monthly Headache Days for IIH patients receiving Exenatide (key hurdle for migraine drug approval is 1.5-2.0 days per month)**
- **Statistically significant & clinically meaningful improvement in visual acuity at 12 weeks, equating to one line improvement on a LogMAR eye chart**
- **Phase II data supports progression to a single Phase III clinical trial for registration in the US and Europe under orphan drug designation starting in 1H 2021**

Invex Therapeutics Ltd (**Invex**, ASX: **IXC,** or the **Company**) today announced the results of the Phase II, double-blind, placebo controlled clinical trial of twice per day Exenatide versus placebo in the treatment of Idiopathic Intracranial Hypertension (IIH).

Professor Alexandra Sinclair, Principal Investigator on the trial, NIHR Clinician Scientist and Neurology Consultant, University Hospital Birmingham NHS Foundation Trust and Executive Director/Chief Scientific Officer of Invex commented "For too long no progress has been made to treat the devastating effects of raised intracranial pressure. I lead one of the largest clinics worldwide for patients with IIH, and having run three of the four previously conducted randomised trials in this debilitating disease am well positioned to recognise the value of this study and the pressing need for effective treatments in IIH. This study provides the first clear evidence that a drug - Exenatide - can significantly reduce ICP in IIH patients. And in particular, the rapidity with which Exenatide lowers ICP is important and will provide a new option to patients whose vision can deteriorate rapidly, and when combined with the sustained benefit and good (drug) tolerability this study will provide renewed optimism to all IIH patients."

Professor Sinclair continued "We know that significant weight loss can also reduce ICP over the longer term and provide clinical benefit in IIH, but this is not an approach that many patients can achieve or sustain, so Exenatide addresses a clear unmet medical need by providing both immediate relief and longer term disease management for IIH patients and their clinicians. This is a major step forward in developing safe and effective therapies to treat IIH patients and the crippling effects of headaches and vision loss on these young, typically female, patients."

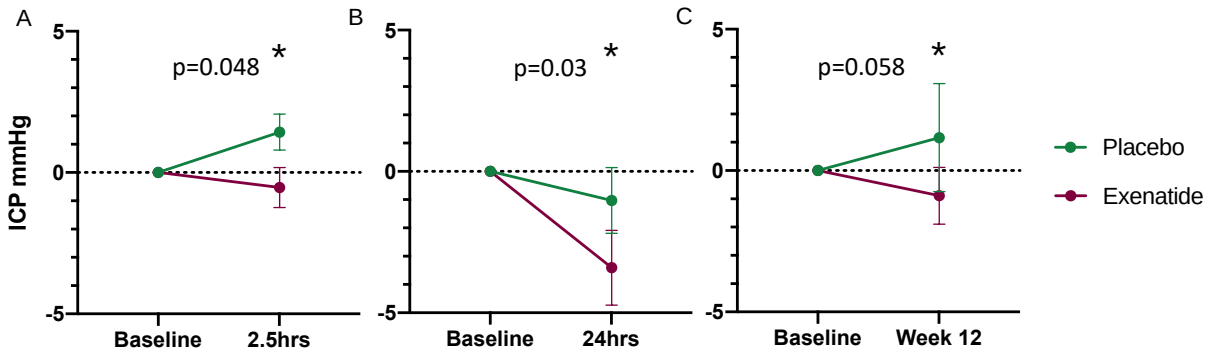
Dr Jason Loveridge, Chairman of Invex commented "These results confirm the safety and potential of Exenatide to reduce intracranial pressure and provide valuable clinical benefit through a reduction in headache frequency and pain medication in IIH patients. These data will be invaluable in the design and execution of our planned single Phase III registration study and increase our confidence that - Presendin™ – Invex's proprietary, patented formulation (of Exenatide) will prove a valuable therapeutic option to patients suffering IIH and who currently have no approved or effective medication."

Primary Endpoints

Under the study design and clinical protocol for this Phase II trial, the study statistician and clinical trial investigators determined the appropriate level of significance was $p<0.10$ and data was analysed by hierarchical regression. Sixteen patients were randomised 1:1 to either Exenatide or placebo, providing 80% power to detect a >10% change in ICP across all three primary endpoints.

The primary endpoints of the study assessed differences in ICP between the Exenatide treatment arm and placebo at; (A) 2.5 hours, (B) 24 hours and at (C) 12 weeks as measured by a surgically implanted Telemetric Intracranial Pressure Monitor providing continuous ICP measurements at 5Hz for 30 minutes at each time point. Each ICP value is the mean of ~9,000 individual pressure measurements in each patient and so provides a very accurate and robust measure of ICP.

These data, summarised in the Figures (A, B, C) below, show that Exenatide reduced ICP at all three time points in a statistically significant manner. Overall, Exenatide use reduced ICP in a rapid and sustained manner by 4.1 - 4.6 mm Hg (5.66 – 6.4 cm H_2O) or 18.1-20.8% compared to placebo.



*Changes in ICP from baseline – mean of each group, Standard Error & *95% CI*

As demonstrated by Sinclair et al[1] 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. On this basis, a reduction of 18.7-21% in IIH patients treated with Exenatide is clearly an important and clinically meaningful outcome.

Secondary Endpoints

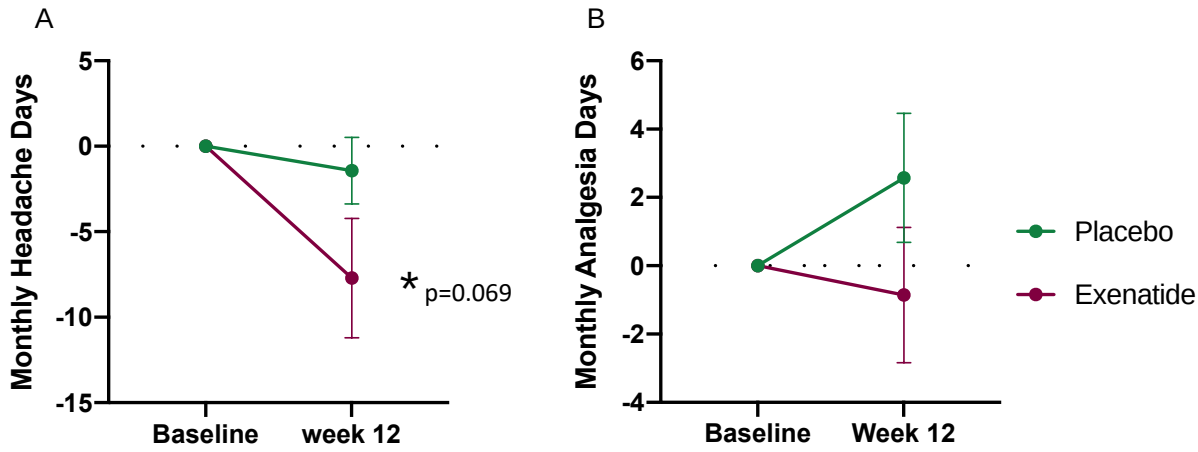
A number of exploratory endpoints were also investigated for their utility as possible primary endpoints in any subsequent Phase III investigation. However, these assessments were not powered to see a statistically significant difference, only to observe a trend towards benefit, and

therefore the results we have seen (and summarised below) indicate a significant drug effect in the IIH cohort.

Headache

Various headache measures were assessed at time 0 and at 12 weeks using standardised tests.

Headache frequency (monthly headache days) data is shown in the Figure A below - highlighting a statistically significant, beneficial reduction in monthly headache days in the Exenatide treated patients. In support of this observation is the data on analgesia use in Figure B, which also shows a trend to reduction in the use of pain medication by IIH patients receiving Exenatide as compared to placebo over the 12 week period of the study.



*Changes in Monthly Headache Days & Monthly Analgesia Days from baseline to week 12 – mean of each group, Standard Error & *95% CI*

The minimal clinically important reduction in monthly headache days has not been established specifically in IIH. However, IIH headaches, while diagnostically distinct (International Classification of Headache Disorders (ICHD-3[2]), share many features such as monthly frequency, with migraine[3], and in migraine the accepted minimal clinically important reduction is 1.5-2 monthly headache days, independent of migraine type – chronic[4,5], episodic[6] or both[7]. Therefore, a reduction of 7.7 days, as seen with Exenatide use over 12 weeks, is clearly clinically meaningful in IIH.

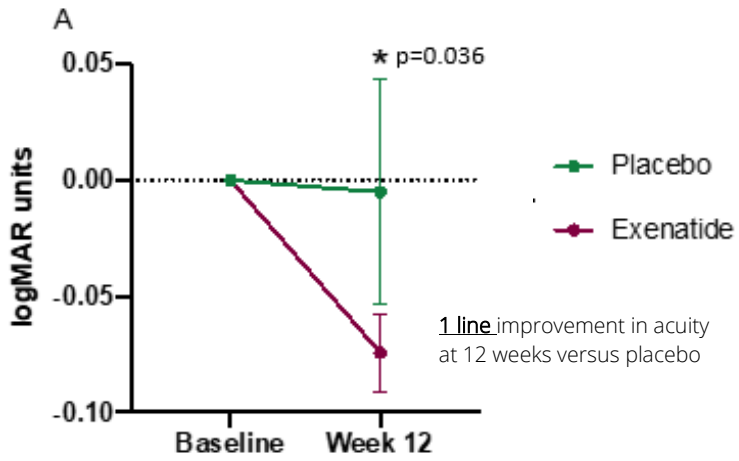
Groups sizes were too small to enable a meaningful comparison between the two groups for headache related quality of life (as measured by the Headache Impact Test (HIT)-6 and SP-36 questionnaires) or headache severity (11-point Verbal Rating Scale) and no meaningful difference between the two groups was observed.

Vision

A number of vision assessments were made at time 0 and 12 weeks utilising standard tests.

Visual acuity was assessed using a Logarithm of the Minimum Angle of Resolution (LogMAR) Chart assessment (Figure A below) and demonstrated a statistically significant improvement (measured as a reduction in LogMAR) in the Exenatide treated arm. Although there has been no

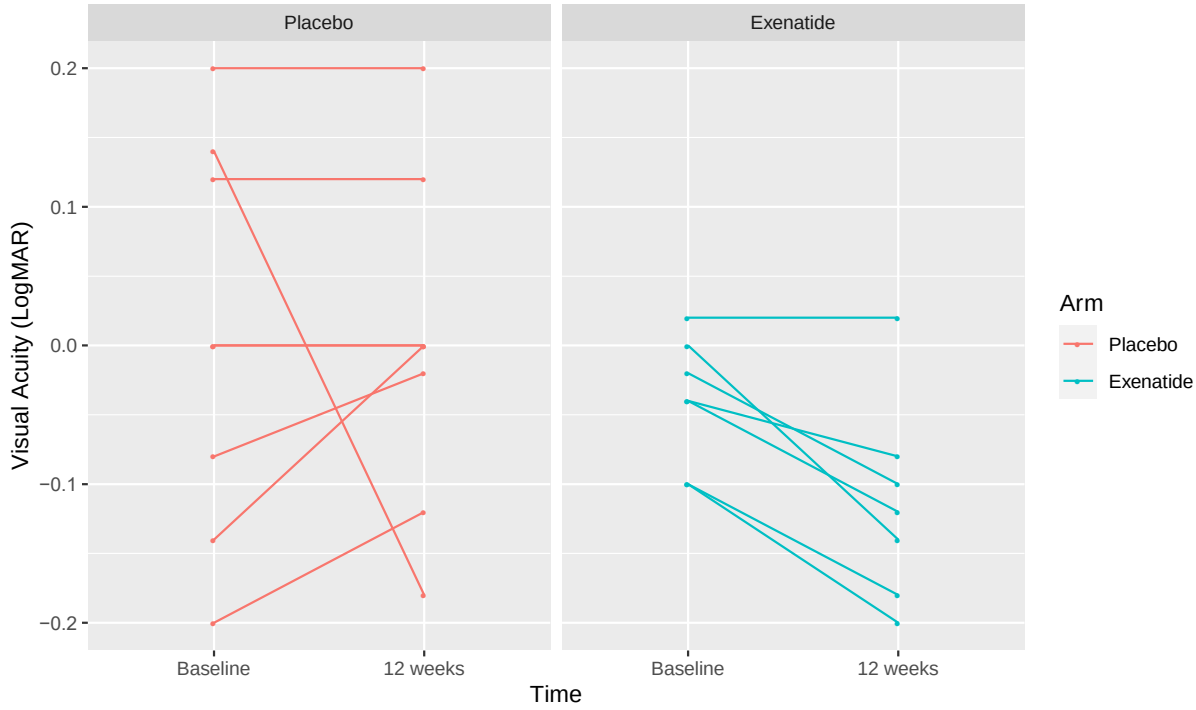
determination of a minimal clinically important improvement in LogMAR in IIH, an improvement equivalent to a whole line (-0.1) on the acuity chart is a significant change for an IIH patient and would be considered a "clinically relevant recovery" by Key Opinion Leaders (KOLs) in the field as well as by patients, for whom such a difference could mean being able to drive or not (for example).



*Changes in LogMAR from baseline to week 12 – mean of each group, Standard Error & *95% CI*

As seen in Figure B below, LogMAR improved in all but one of the Exenatide treated patients and in only a single patient on placebo, further supporting the breadth and clinical relevance of the improvement to patients' vision seen with Exenatide.

Figure B

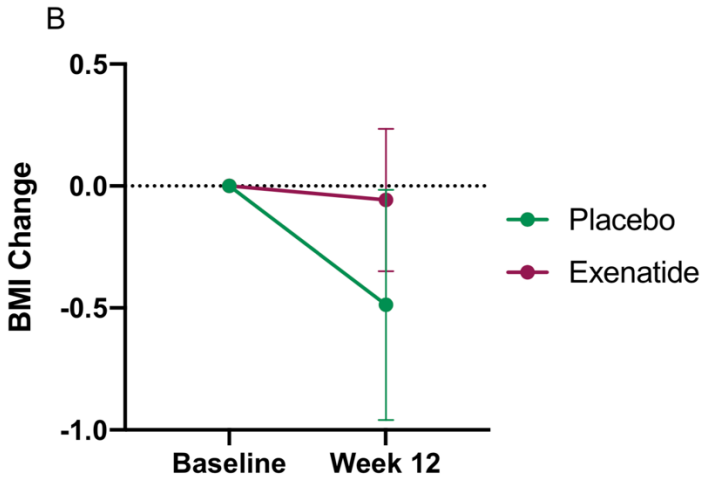


No difference was observed between the two groups for Humphrey Visual Field, although this is not surprising given that 12 weeks – according to the Company's Advisory Board – is a relatively short period of time to see an improvement in perimetric mean deviation (visual field), and in

Sinclair et al[1] a reduction in ICP over 12 weeks also did not lead to an improvement in patients' visual field.

Body Mass Index (BMI)

BMI was measured at the beginning and end of the study (12 weeks) and as seen in the Figure B below did not change significantly throughout the study confirming that the reduction in ICP and clinical benefit seen through the use of Exenatide was not a result of weight loss in the treatment arm.



Changes in BMI from baseline to week 12 – mean of each group, Standard Error

All current clinical guidelines for treatment of IIH recommend significant weight loss as the only effective disease modifying treatment for IIH at present and Sinclair et al[1] demonstrated that a reduction of 15% in total body mass (low energy diet – 425kcal/day) is required to meaningfully reduce the symptoms of IIH where a 16.5% (6.2 cmH_2O) reduction in ICP (above that observed with no intervention) resulted in a statistically significant improvement in headache and vision measures as well as quality of life.

Safety & Adverse Events

No serious adverse events were observed relating to the use of Exenatide. Overall, adverse events were relatively low, with nausea the most common seen in 38% of patients treated with Exenatide. Nausea is a known and the most frequent adverse event of sub-cutaneous administration of this formulation of Exenatide (Byetta®).

Currently the most widely used drug (in IIH) - acetazolamide - is discontinued in ~48% of patients due to intolerable side effects[8] whereas no patients withdrew from the current study due to side-effects from Exenatide use. Acetazolamide is not approved in any market for the treatment of IIH.

Event	Number & Arm*	Description
Serious Adverse Events (SAE)	1, P	Thyrotoxicosis (unrelated, participant continued in study)
Adverse Events (AE)	3, E	Nausea – required treatment
	4, E	Nausea – mild transient
	1, E 2, P	Minor wound infection (unrelated, participant continued in study)
	1, E	Post-operative swelling

*P = Placebo, E = Exenatide

Patient Baseline Characteristics

As can be seen from the Table below, the patients were well balanced at baseline with the only significant difference between the groups (at baseline) being with respect to monthly headache days where the difference was skewed by two patients in the placebo group with very low monthly headache days at baseline. There was no significant difference in any other measure, including: BMI, ICP or visual acuity between the arms at baseline.

	Exenatide		Placebo		Differences	
	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Wilcoxon rank sum p	chi-squared p
Number	7		8			
Age	25 (18, 57)	28 (13)	26 (23, 38)	28 (6)	0.560	
Gender (% female)	100		100			
BMI (kg/m2)	35.5 (31.3, 54.4)	37.6 (7.9)	39.9 (29.4, 44.2)	38.6 (4.7)	0.281	
ICP (mmHg)	21.9 (17.4, 28.5)	22.3 (3.6)	24.2 (19.3, 30.2)	24.6 (4.1)	0.281	
Monthly Headache Days	21 (13, 28)	22 (5)	12 (0, 21)	10 (9)	0.015*	
Monthly analgesic frequency	7 (3, 16)	7.9 (4.5)	3 (0, 8)	3.4 (2.8)	0.054	
Headache severity (VRS 0-10)						
Category 1						0.133
Mild, n (%)	0 (0%)		3 (38%)			
Moderate	6 (86%)		5 (62%)			
Severe	1 (14%)		0 (0%)			
LogMar visual acuity	0.0 (-0.1, 0.0)	0.0 (0.1)	0.0 (-0.2, 0.2)	0.0 (0.1)	0.522	
Perimetric mean deviation worst eye dB (HVF 24-2 Sita standard)	-0.4 (-2.5, 0.3)	-0.6 (1.0)	-2.5 (-5.1, 0.5)	-2.7 (1.9)	0.072	
Optical Coherance Tomography RNFL wost eye (um)	128 (91, 236)	153 (59)	161 (85, 337)	183 (100)	0.852	
Headache disability (HIT-6)						0.218
Little-to-no impact, n (%)	0 (0%)		2 (25%)			
Moderate	0 (0%)		1 (13%)			
Severe	5 (71%)		2 (25%)			
Substantial	2 (29%)		3 (38%)			
Quality of Life (SF-36) **PCS summary** **MCS summary**	 53.5 (10.2, 71.9) 46.1 (7.5, 67.0)	 50 (20) 43 (23)	 59.1 (26.7, 80.2) 49.7 (26.0, 75.5)	 58 (17) 47 (17)	 0.418 0.852	
Creatinine (µmol/L)	69 (51, 77)	68 (9)	69 (48, 72,)	66 (8)	0.601	
ALT (IU/L)	22 (15, 45)	27 (14)	16 (12, 46)	21 (12)	0.363	
HDL (mmol/L)	1.15 (0.73, 1.82)	1.26 (0.36)	1.49 (1.18, 1.82)	1.48 (0.24)	0.117	
Cholesterol (mmol/L)	4.5 (3.7, 5.9)	4.53 (0.79)	4.2 (3.7, 6.2)	4.76 (1.0)	0.727	
Triglycerides (mmol/L)	1.0 (0.6, 2.2)	1.26 (0.65)	1.2 (0.9, 1.4)	1.14 (0.18)	0.907	
HbA1c (mmol/mol)	37 (32, 38)	35.4 (2.7)	37 (29, 38)	35.0 (3.9)	1.000	

*Significant difference at 5% level

The study investigators intend to submit the clinical data to a leading scientific publication for peer-review in due course and to present the data at the 4th European Headache Federation Congress (June 29 – July 02, 2020).

Conclusions

We believe these Phase II data strongly support moving Presendin™ into a Phase III clinical trial (1H of 2021). The study provided clear statistical and clinical evidence of efficacy in the primary and in some key secondary endpoints and demonstrates both an immediate reduction in ICP and a strong and sustained clinical benefit in the IIH cohort at 12 weeks. This study provides the first evidence that Exenatide can significantly reduce ICP in IIH patients.

The Company would like to acknowledge and thank the study investigators and most particularly the patients for participating in this first of a kind clinical trial in IIH.

References quoted in this Press Release

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2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* **38**, 1–211 (2018).
3. Mollan S P et al., Curr Opin Neurol. 2019 Feb;32(1):92-98
4. Tepper et al., Lancet Neurol. 2017 Jun;16(6):425-434
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6. Goadsby et al., Goadsby et al., 2017
7. Camporeale et al., Camporeale et al., 2018
8. Ball AK et al., 2011 May;258(5):874-81

This release dated 20th May has been authorised for lodgement to ASX by the Board of Directors of Invex Therapeutics and lodged by Narelle Warren, Company Secretary.

ENDS

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About Invex Therapeutics Ltd

Invex is a biopharmaceutical company focused on the repurposing of an already approved drug, Exenatide, for efficacious treatment of neurological conditions derived from or involving raised intracranial pressure, such as Idiopathic Intracranial Hypertension (IIH), acute stroke and traumatic brain injury. Invex has trademarked its repurposed Exenatide as Presendin™. www.invextherapeutics.com.

About Idiopathic Intracranial Hypertension (IIH)

IIH features severely raised intracranial pressure which causes disabling daily headaches and can compress the optic nerve, causing permanent vision loss in 25% of those affected. The usual age of onset is 20-30 years, and it is most common in women who are obese. IIH is a rapidly growing orphan indication: its incidence has increased by more than 350% in the last 10 years.

About Exenatide

Exenatide is a small peptide and a synthetic version of the GLP-1 agonist exendin-4, which received approval in the US and Europe for the treatment of type 2 diabetes in 2005 and 2006 respectively. Professor Alexandra Sinclair's research showed that GLP-1 receptors are expressed in the choroid plexus in the brain and that Exenatide can bind to these receptors and reduce secretion of cerebrospinal fluid. Current Exenatide dosage forms are not optimised for IIH.

About Exenatide IIH Clinical Trial

The Exenatide clinical trial in IIH is a single centre, randomised Phase II, double-blind, placebo-controlled clinical trial in 16 patients with active IIH comparing sub-cutaneous (s.c.) 10 µg Exenatide twice daily with placebo. The primary endpoint of the study is the change in intracranial pressure over 12 weeks of dosing as measured by real-time patient monitoring devices.

The *Inclusion* Criteria for the study were as follows: female, aged 18-60 years old, diagnosed with IIH by the modified Dandy criteria, active disease (papilloedema Frisen grade greater than 1), significantly raised ICP (greater than 25cm CSF), no evidence of venous sinus thrombosis (documented normal MR Venogram of CT Venogram) and able to provide informed consent.

The *Exclusion* Criteria for the study were as follows: aged less than 18 or older than 60 years, pregnant or trying to conceive, significant co-morbidity, such that in the opinion of the investigator it would not be in the participant's best interest to participate in the trial, Addison's or Cushing's disease, functioning CSF shunt/stent or optic nerve sheath fenestration, currently using GLP-1 agonist or DPP-4 inhibitor, surgical contra-indication, concomitant therapy with acetazolomide, topiramate or diuretics (this can be discontinued 1 month prior to enrolment), or inability to give informed consent e.g. due to cognitive impairment.