Repurposing Exenatide for Orphan Neurological Condition

Invex Therapeutics is in late-stage development of a proprietary, once-weekly formulation of Exenatide, branded Presendin™, to treat diseases caused by raised intracranial (brain) pressure (ICP). This follows clinical evidence that Exenatide, a drug previously approved to treat type 2 diabetes, can also lower ICP by reducing cerebrospinal fluid secretion. Invex is currently evaluating the efficacy of Presendin™ to treat idiopathic intracranial hypertension (IIH), an orphan disorder that results from raised ICP.

Chronic Disease with High Unmet Need

IIH is a chronic disorder largely affecting young, obese women. It can have serious clinical effects (from daily headaches to loss of sight, which can be permanent), and despite off-label use of some drugs, it has no approved treatment based on clinical evidence. Total addressable market (US + Europe + UK) is estimated at ~A$1.6b for IIH.

Orphan Drug Designation Granted

Exenatide has received orphan drug designation for the treatment of IIH, giving 10 years' market exclusivity in Europe and 7 years' exclusivity in the US upon launch.

Phase 3 IIH EVOLVE Clinical Trial – Designed for Global Market Approval

A Phase 3, 240-patient clinical trial (IIH EVOLVE) has been designed to meet the requirements for market approval of Presendin™ for treating IIH in the EU, UK, and Australia, and inform its market approval process for the FDA. The trial, across 37 centres, aims to enrol the first patient in late 1HCY22. Only 1 Phase 3 trial will be required (vs. 2 for traditional drug developers), lowering risks and costs.

Peptron Deal Adds Clinical Synergies

Invex has signed a long-term collaboration and manufacturing agreement with Korea-based biopharm Peptron to advance Exenatide in neurological conditions caused by ICP. Peptron has extensive preclinical/clinical data on a long-acting formulation of Exenatide and a purpose-built GMP manufacturing site with capacity to produce >48,000 vials per month.

Invex Therapeutics Limited is an ASX-listed clinical stage biopharmaceutical focused on the development of Exenatide as a treatment for neurological conditions arising from or involving increased intracranial pressure. This includes a late-stage Phase 3 development program in idiopathic intracranial hypertension (IIH) and new potential disease indications related to raised intracranial pressure under consideration.

Stock	IXC.ASX
Price	A$0.58
Market cap	A$44m
Valuation	A$3.38

Company data	
Net cash (as at 31 Dec 2021)	$31.4m
Shares on issue	75.2m
Code ASX	IXC

Share price catalysts
1HCY22: Regulatory filings and approvals to commence Phase 3 progressively (US, EMA, MHRA, HREC) in UK, Europe, Australia, US
Late 1HCY22: Phase 3 commencement (first patient)

IXC share price (A$)

Source: FactSet.

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Multiple Neurological Indications Provide Broader Future Potential

ICP is implicated in multiple serious neurological conditions, including clots and blockages, traumatic brain injury, brain tumours, infections leading to meningitis, and stroke. We view Invex's focus on IIH as a strategic gateway indication that could lead to development of treatments for other indications.

Valuation: A$3.38 Per Share Using Risk-Adjusted NPV Method

We value Invex Therapeutics at A$254m (A$3.38 per share) on an undiluted basis, using a risk-adjusted NPV method to discount future cash flows through to 2035. Risks relate to Invex's single drug focus, although we think these are mitigated by its orphan drug status, late-stage development phase and market opportunity.

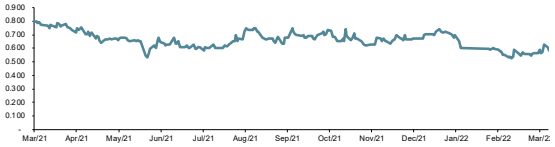
Financial Summary

Invex Therapeutics Ltd IXC-AU

Year end 30 June, AUD unless otherwise noted

MARKET DATA		
Price	**$**	**0.58**
52 week high / low	$	0.53-0.85
Valuation	**$**	**3.38**
Market capitalisation	$m	43.6
Shares on issue (basic)	**m**	75.2
Options / rights	m	4.6
Other equity	m	0.0
Shares on issue (diluted)	**m**	**79.8**

12-MONTH SHARE PRICE PERFORMANCE (A$)



INVESTMENT FUNDAMENTALS		FY20A	FY21A	FY22E	FY23E	FY24E
Reported NPAT	$m	(3.4)	(2.3)	(5.2)	(7.2)	(11.2)
Underlying NPAT	**$m**	**(3.4)**	**(2.3)**	**(5.2)**	**(7.2)**	**(11.2)**
Reported EPS (diluted)	¢	(6.0)	(3.0)	(6.9)	(9.6)	(14.9)
Underlying EPS (diluted)	**¢**	**(6.0)**	**(3.0)**	**(6.9)**	**(9.6)**	**(14.9)**
Growth	%		-49.2%	126.7%	39.0%	55.9%
Underlying PER	x	**nm**	**nm**	**nm**	**nm**	**nm**
Operating cash flow per share	¢	(2.9)	(2.2)	(6.8)	(9.5)	(14.9)
Free cash flow per share	¢	(2.9)	(2.2)	(6.8)	(9.5)	(14.9)
Price to free cash flow per share	**x**	**nm**	**nm**	**nm**	**nm**	**nm**
FCF Yield	%	nm	nm	nm	nm	nm
Dividend	¢	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Payout	%	0.0%	0.0%	0.0%	0.0%	0.0%
Yield	**%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**	**0.0%**
Franking	%	0.0%	0.0%	0.0%	0.0%	0.0%
Enterprise value	**$m**	**17.3**	**10.9**	**16.0**	**23.2**	**34.4**
EV/EBITDA	x	(8.2)	(6.3)	(3.5)	(3.5)	(3.2)
EV/EBIT	x	(8.2)	(6.3)	(3.5)	(3.5)	(3.2)
Price to book (NAV)	x	1.6	1.4	1.6	2.2	5.1
Price to NTA	x	1.6	1.4	1.6	2.2	5.1

KEY RATIOS		FY19A	FY20A	FY21A	FY22E	FY23E
ROE	%	nm	nm	nm	nm	nm
ROA	%	nm	nm	nm	nm	nm
Net tangible assets per share	$	0.4	0.4	0.4	0.3	0.1
Book value per share	$	0.0	0.0	0.0	0.0	0.0
Net debt/(cash)	$m	(26.3)	(32.7)	(27.6)	(20.4)	(9.2)

DUPONT ANALYSIS		FY19A	FY20A	FY21A	FY22E	FY23E
Return on Assets	%	nm	nm	nm	nm	nm
Leverage	x	1.1	1.0	1.0	1.0	1.1
Return on Equity	%	nm	nm	nm	nm	nm

KEY PERFORMANCE INDICATORS	FY19A	FY20A	FY21A	FY22E	FY23E
IIH EVOLVE Phase 3 trial	Regulatory filings and approvals to commence Phase 3 patient enrollment				

HALF YEARLY DATA		2H21	1H22	2H22	1H23	2H23
Other income	$m	0.0	0.2	(0.1)	0.1	0.1
Operating expenses	$m	(1.0)	(1.8)	(3.0)	(3.3)	(3.3)
EBITDA	$m	(0.9)	(1.5)	(3.1)	(3.2)	(3.2)
EBIT	$m	(0.9)	(1.5)	(3.1)	(3.2)	(3.2)
PBT	$m	(1.2)	(1.8)	(3.4)	(3.2)	(3.2)
Reported NPAT	$m	(1.2)	(1.8)	(3.4)	(3.2)	(3.2)

PROFIT AND LOSS		FY20A	FY21A	FY22E	FY23E	FY24E
Other income	**$m**	**0.2**	**0.2**	**0.2**	**0.2**	**0.2**
Operating expenses	$m	(2.3)	(1.9)	(4.8)	(6.8)	(10.8)
EBITDA	**$m**	**(2.1)**	**(1.7)**	**(4.6)**	**(6.6)**	**(10.7)**
Depreciation & Amortisation	$m	0.0	0.0	0.0	0.0	0.0
EBIT	**$m**	**(2.1)**	**(1.7)**	**(4.6)**	**(6.6)**	**(10.7)**
Net interest	$m	0.0	0.0	0.0	0.0	0.0
Pretax Profit*	**$m**	**(3.4)**	**(2.3)**	**(5.2)**	**(7.2)**	**(11.2)**
Tax expense	$m	0.0	0.0	0.0	0.0	0.0
Reported NPAT	**$m**	**(3.4)**	**(2.3)**	**(5.2)**	**(7.2)**	**(11.2)**
Weighted average diluted shares	m	56.2	75.2	75.2	75.2	75.2

*Includes share-bsed payments (not included in EBIT)

GROWTH PROFILE		FY20A	FY21A	FY22E	FY23E	FY24E
Other income	%	125,432.6	(4.2)	5.0	5.0	5.0
EBITDA	%	1,553.4	(18.0)	168.1	43.8	60.6
EBIT	%	1,553.4	(18.0)	168.1	43.8	60.6
Reported NPAT	%	1,347.6	(32.0)	126.7	39.0	55.9

BALANCE SHEET		FY20A	FY21A	FY22E	FY23E	FY24E
Cash	$m	26.3	32.7	27.6	20.4	9.2
Receivables	$m	0.1	0.0	0.0	0.0	0.0
Current assets	**$m**	**26.4**	**32.7**	**27.6**	**20.4**	**9.2**
Intangible assets	$m	0.0	0.0	0.0	0.0	0.0
Non current assets	**$m**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Total assets	**$m**	**26.4**	**32.7**	**27.6**	**20.4**	**9.2**
Trade and other payables	$m	0.7	0.7	0.7	0.7	0.8
Other	$m	1.3	0.0	0.0	0.0	0.0
Current liabilities	**$m**	**2.0**	**0.7**	**0.7**	**0.7**	**0.8**
Total liabilities	**$m**	**2.0**	**0.7**	**0.7**	**0.7**	**0.8**
Net assets	**$m**	**24.4**	**32.1**	**26.9**	**19.7**	**8.5**
Share capital	$m	27.0	36.4	36.4	36.4	36.4
Retained earnings	$m	(3.6)	(5.9)	(11.1)	(18.3)	(29.5)
Other	$m	1.0	1.5	1.5	1.5	1.5
Total equity	**$m**	**24.4**	**32.1**	**26.9**	**19.7**	**8.5**

CASH FLOW		FY20A	FY21A	FY22E	FY23E	FY24E
Net loss for period	**$m**	**(3.4)**	**(2.3)**	**(5.2)**	**(7.2)**	**(11.2)**
Depreciation & Amortisation	$m	0.0	0.0	0.0	0.0	0.0
Changes in working capital	$m	0.7	0.0	0.0	0.0	0.0
Other	$m	1.1	0.6	0.0	0.0	0.0
Operating cash flow	**$m**	**(1.6)**	**(1.7)**	**(5.1)**	**(7.2)**	**(11.2)**
Payments for PPE	$m	0.0	0.0	0.0	0.0	0.0
Investing cash flow	**$m**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Capital raising costs	$m	(1.8)	(0.6)	0.0	0.0	0.0
Subscription proceeds	$m	17.6	8.6	0.0	0.0	0.0
Financing cash flow	**$m**	**15.7**	**8.1**	**0.0**	**0.0**	**0.0**
Cash year end	**$m**	**26.3**	**32.7**	**27.6**	**20.4**	**9.2**
Free cash flow	**$m**	**(1.6)**	**(1.7)**	**(5.1)**	**(7.2)**	**(11.2)**

Source: Company, MST Access.

Thesis: Targeting Brain Pressure–Related Neurological Indications

Company Profile: Repurposing Exenatide with Proprietary Formulation

Invex Therapeutics is a biopharmaceutical company focused on developing treatments for neurological conditions resulting from or involving raised intracranial pressure (ICP).

Invex's purpose: treating raised intracranial pressure

ICP can occur due to a number of conditions, including clots and blockages, traumatic brain injury, brain tumours, infections leading to meningitis, and stroke. Invex is currently focused on ICP caused by idiopathic intracranial hypertension (IIH), a rare but increasing condition with poor treatment options and serious side effects found most commonly in women with obesity aged 15–60.

Invex was founded to advance research conducted at the University of Birmingham, UK, by Dr Alexandra J Sinclair in brain pressure–related neurological disorders. Dr Sinclair demonstrated in animal models and subsequently in IIH patients that Exenatide, a drug that has already been approved for therapeutic use in humans by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes, can reduce ICP. Dr Sinclair, a clinician and global leader in the treatment and pathophysiology of IIH, is Executive Director and Chief Scientific Officer of Invex.

Strategy: a new use for an existing drug to target raised ICP

Lead asset Exenatide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) first approved in 2005 for the treatment of type 2 diabetes and sold under the brand names Byetta® and Bydureon®. Exenatide is well tolerated and considered a standard of care in type 2 diabetic patients. Invex is focused on repurposing Exenatide using a proprietary formulation to treat conditions characterised by raised ICP where it has shown strong data in both animal and human clinical trials to date. Repurposing Exenatide through drug reformulation provides a lower risk approach to its development, and potentially lower cost and shorter route to market.

Specifically, Exenatide is being developed to treat IIH, an orphan disease, in the first instance. The condition results in raised pressure in the brain and can cause daily headaches and loss of sight by compressing the nerves to the eye (papilloedema).

Potential Near-Term Catalysts

- Ethics approval to commence IIH EVOLVE Phase 3 trial in Australia
- First patient enrolled in IIH EVOLVE Phase 3 trial in Australia
- Medicines and Healthcare Products Regulatory Agency (MHRA) UK clinical trial application (CTA) to commence Phase 3 in the UK
- European Medicines Agency (EMA) CTA to commence Phase 3 in Europe
- IND submission to FDA to commence Phase 3 trial in the US

Financials

The company is essentially structured as a virtual business with a small number of key personnel based in the UK engaging additional expertise of clinical, regulatory, and manufacturing consultants as required. As such the costs are relatively low and largely driven by the funding of clinical development of Presendin™ which, subject to ethics approval, will commence a Phase 3 registration study in 1HCY22.

Valuation

We value Invex Therapeutics at A$254m (A$3.38 per share) on an undiluted basis, using a risk-adjusted NPV method to discount future cash flows through to 2035.

Risks and Sensitivities

Despite Exenatide's orphan drug designation status, late-stage development phase and attractive market opportunity, Invex's single drug development program focus exposes investors to several key risks, both company-specific and related to the biotech sector more broadly (see Sensitivities and Risks section).

The Science of Presendin™: Reformulating Exenatide for Neurological Indications

The Goal: Leveraging Exenatide's Orphan Drug Designation in IIH – Market Exclusivity and a Potential Gateway to Other Indications

Invex Therapeutics is an ASX-listed clinical-stage biopharmaceutical company focused on the development of Exenatide as a treatment for neurological conditions involving increased intracranial pressure (ICP), with a focus on idiopathic intracranial hypertension (IIH). Other conditions involving raised ICP include clots and blockages, traumatic brain injury, brain tumours, infections leading to meningitis, and stroke.

Invex listed on the ASX in 2019, raising $12m, to commercialise intellectual property created by Dr Alexandra Sinclair at the University of Birmingham, UK. Dr Sinclair's research group at the university examined the effects of the natural form of Exenatide, exendin-4 (found in the saliva of the Gila monster)[1], in reducing cerebrospinal fluid (CSF) secretion, demonstrating this effect in both animal tissue/cells and animal models.

Invex is now focused on leveraging strong Phase 2 clinical data for Exenatide in the treatment of IIH, for which it has orphan drug designation, to move into a pivotal trial. This could see the drug reach the market by end-CY25, subject to positive clinical results. As such, we view IIH as the gateway indication which, when combined with the orphan drug designation it has in both Europe and the US, would give it a respective 10 and 7 years of market exclusivity in these markets.

Exenatide's Clinical History: First-In-Class Anti-Diabetic Drug Approved in 2005

Background to use of GLP-1 therapies in diabetes. Naturally occurring glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are intestinal peptide hormones released after meals, mainly in response to glucose and fat, that help regulate insulin secretion in the pancreas. GLP-1 was discovered in the 1980s and, along with GIP which was discovered in the early 1970s, classified as an incretin hormone. Endogenous or naturally occurring GLP-1 is produced in the small intestine and stimulates insulin secretion and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner. Unlike GIP, GLP-1 showed potential to trigger insulin production in the pancreas and inhibit glucagon secretion in patients with type 2 diabetes, leading to the clinical development of GLP-1 agonists[2].

What is Exenatide? Exenatide is a first-in-class glucagon-like peptide-1 receptor agonist (GLP-1 RA), approved for the treatment of type 2 diabetes. It belongs to a class of drugs called incretin mimetics, so called because they work by mimicking the body's naturally occurring incretin hormones.

What is the mechanism of action for Exenatide in treating type 2 diabetes? Exenatide is a small peptide synthetic version of exendin-4, a protein found in the saliva of the Gila monster that mimics GLP-1 and therefore classified as a GLP-1 RA. GLP-1 RAs such as Exenatide work by binding to GLP-1 receptors in the pancreas, enhancing insulin release and reducing glucagon release-responses that are both glucose-dependent and as a result carry a lower risk of hypoglycaemia[3].

How has Exenatide been used in the past? Exenatide was approved in 2005 in the US and 2006 in the EU for the treatment of type 2 diabetes under the brand name Byetta® for administration as a twice-daily subcutaneous injection. In 2012, the FDA-approved Bydureon® (Exenatide in an extended-release formula) as a the first once-weekly injectable treatment. It is used to control blood sugar in type 2 diabetics (as an adjunct to diet and exercise) who have not achieved adequate control on metformin and/or sulfonylurea, two commonly prescribed oral diabetic medications. AstraZeneca reported FY21 sales for Bydureon® and Byetta® of US$385m and US$55m, respectively, in effect providing a proxy for drug safety and efficacy.

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[1] The desert-dwelling Gila monster (Heloderma suspectum) is the United States' largest and only native venomous lizard. (https://www.nhm.ac.uk/discover/the-monster-whose-bite-saves-lives.html#:~:text=The%20desert%2Ddwelling%20Gila%20monster,warning%20to%20would%2Dbe%20predators.)

[2] From the Incretin Concept and the Discovery of GLP-1 to Today's Diabetes Therapy: Holst (2019)

[3] https://pubmed.ncbi.nlm.nih.gov/26371721/

New Role for Exenatide: Diuretic and Novel Targeted Therapy for Raised ICP

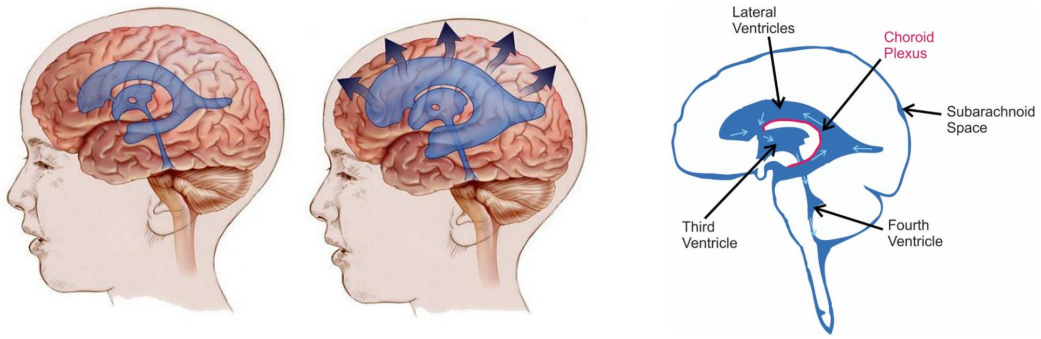
In 2017, research conducted by Dr Sinclair's group at the University of Birmingham looked at the effect of GLP-1 RAs, such as exendin-4 (the naturally occurring form of the synthetic compound Exenatide), on cerebrospinal fluid (CSF) secretion at the choroid plexus. These findings established both a new mechanism of action for Exenatide, and a potentially novel therapeutic approach to reducing CSF secretion to treat raised ICP, by targeting GLP-1 receptors (GLP-1 Rs) in the choroid plexus.

Targeting the choroid plexus. The choroid plexus is a complex network of capillaries lined by specialised cells which produces most of the central nervous system's CSF and serves as a conduit between the peripheral circulation and the brain. CSF volume is tightly regulated and depends on the balance between CSF secretion and CSF drainage. CSF is secreted by the epithelial cells of the choroid plexus and regulated by net movement of sodium ions (Na+) from the blood into the ventricles of the brain.

What is the mechanism of action for Exenatide in treating raised ICP? Although the mechanism by which ICP is elevated is not clear, it is thought to be multifactorial and largely driven by excess CSF produced in the choroid plexus. The proposed use of GLP-1 RAs in neurological disorders involving raised ICP stems from an alternate mechanism of action on GLP-1 receptors in the choroid plexus as a diuretic.

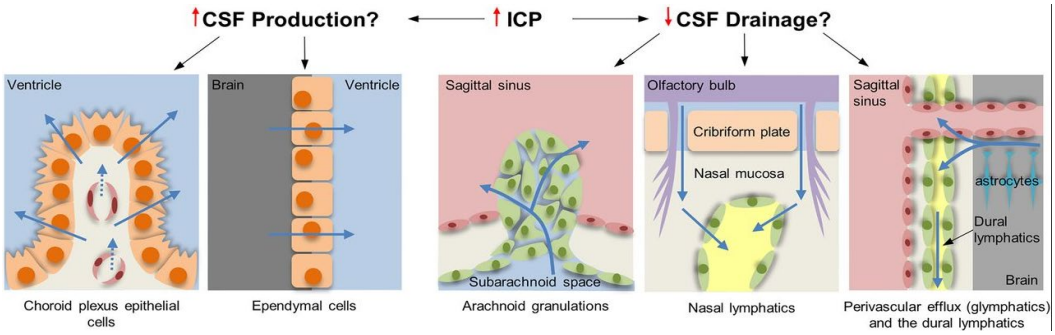
How did Dr Sinclair's research validate this mechanism of action? Dr Sinclair's research demonstrated that GLP-1 receptors are expressed in the choroid plexus region of the brain and that GLP-1RAs lowered ICP in hydrocephalus rat models[4]. The findings suggested that the GLP-1 receptors expressed in the choroid plexus, when stimulated, trigger a diuretic effect by modulating sodium (Na+) transport to create an osmotic gradient driving the movement of water, thereby regulating fluid movement, and reducing ICP. Confirmation that this effect was due to the expression and activation of GLP-1 receptors in the choroid plexus was achieved using a GLP-1 **ant**agonist (which works to counteract the GLP-1 RA).

Exhibit 1: Repurposing Exenatide to treat raised ICP by targeting the choroid plexus



Source: Marketresearchfuture: https://www.openpr.com/news/1140007/pseudotumor-cerebri-idiopathic-intracranial-hypertension-market-is-growing-in-europe-a-growing-concern-industry-report-segmented-by-diagnosis-treatment-region-and-key-players.html.

Exhibit 2: Mechanism of action: targeting GLP-1 receptors in choroid plexus to reduce production of CSF



Source: https://jnnp.bmj.com/content/87/9/982.

[4] A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus: Botfield et al

The Opportunity: Major Unmet Need to Treat Orphan Disease (Idiopathic Intracranial Hypertension) with Poor Current Options

Invex Therapeutics is currently assessing the potential for subcutaneous injection of lead asset Presendin™ to treat patients with idiopathic intracranial hypertension.

IIH: A Growing Problem, an Attractive Market Opportunity

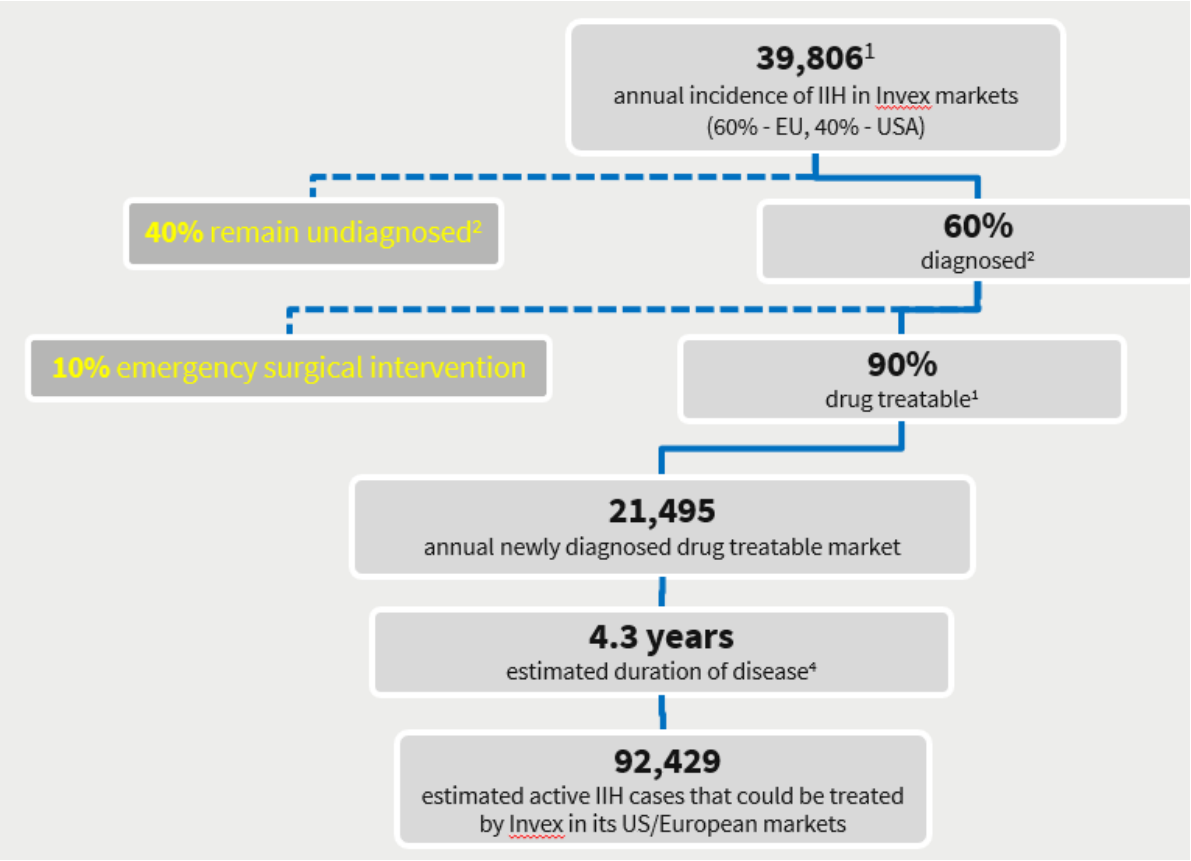
Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a rare condition of unknown cause characterised by elevated ICP related to high levels of CSF. 'Intracranial hypertension' refers to a build-up of pressure within the skull. 'Idiopathic' means simply that the cause is unknown. This increase in pressure on the brain often results in:

- daily headaches
- papilloedema (swelling of the optic nerve)
- loss of sight, which can be permanent in 25% of cases.

Other visual, aural, and cognitive symptoms, as well as back and neck pain, can also occur.

There is a significant unmet medical need for the treatment of IIH, for which there are no approved medical treatments. As such, we see IIH as an attractive market opportunity, for which Invex has been awarded orphan drug designation in both Europe and the USA.

Exhibit 3: Total addressable market (TAM) is expected to grow

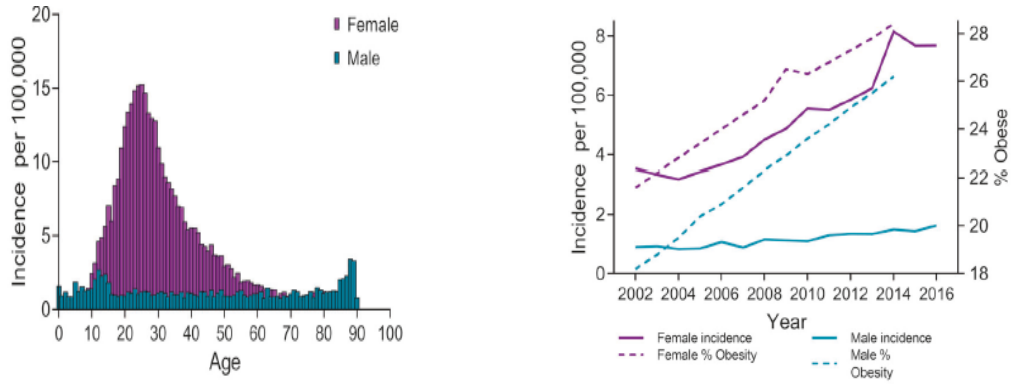


(1). Mollan et al., The expanding burden of idiopathic intracranial hypertension (2019) incidence rate of 4.7/100,000 general population, n=23,182. Target markets are EU 27(& UK) + USA. (2). Mollan SP, et al. Idiopathic intracranial hypertension: consensus guidelines on management (2018); Invex estimate re % presenting headache severity. (3). Simoens et al., "What price do we pay for repurposing drugs for rare diseases?" (2016) – average 66x & Invex initial pricing analysis => pricing subject to change. (4). D. Friesner et al., Idiopathic intracranial hypertension in the USA: the role of obesity in establishing prevalence and healthcare costs (2010). (5). Assumes average of obesity growth rates in UK and historical incidence growth rate. Source: Invex Therapeutics.

Incidence – rare but affects mostly women and growing in line with rising levels of obesity

The annual incidence of IIH is 1–2 per 100,000 population[5]. Although the underlying pathogenesis of IIH is uncertain, it is significantly more common in women between the ages of 15 and 44 years (average onset age: 20–30 years) who are obese (4–21 per 100,000: see Exhibit 4). Further, recent studies suggest IIH patient incidence is rising in parallel with obesity rates (see Exhibit 4)[6].

Exhibit 4: Incidence by age, sex, and obesity rates (based on UK studies)



Source: The expanding burden of idiopathic intracranial hypertension: Mollan et al (2018).

Diagnosis of IIH – challenging due to unclear early signals and lack of awareness

Early diagnosis and treatment of IIH are important to prevent permanent visual loss. However, diagnosis can be challenging as the condition is rare and early symptoms highly variable (typically, severe headaches and papilloedema) and often sporadic, leading to delays in identification. Further, other medical conditions or medications can give rise to elevated ICP, so-called secondary intracranial hypertension, including meningitis, brain tumours, tetracyclines and corticosteroids. As such, diagnosis of IIH is made after other causes have been excluded.

Symptoms of IIH include chronic headaches that can have a severe impact on quality of life, pulsatile tinnitus, back and radicular pain, dizziness, cognitive disturbances, and diplopia (double vision). The major challenge with IIH is that its key symptoms are not unique to the condition. Historically, the diagnostic criteria for IIH require excluded secondary causes in order to get to a definitive IIH diagnosis. That said, Dr Sinclair helped develop and co-author consensus treatment guidelines for IIH, which were published and adopted widely in 2018. As such, we think awareness of IIH should increase and expect diagnosis will generally trend higher. Currently most IIH patients present at either Accident & Emergency departments or opticians and are referred to a neurologist and neuro-ophthalmologist for diagnosis and treatment.

Current Treatment Options Have Limited Efficacy and Tolerability

Effective treatment is an unmet clinical need in IIH and represents the market opportunity for Presendin™. Current guidelines for managing IIH are contingent on the severity of the condition in patients with imminent threat to loss of vision. Management of less severe cases of IIH, with no immediate threat to vision, focuses on lifestyle modifications supporting weight loss, given the strong association with obesity, coupled with the use of various medications, albeit with limited efficacy to reduce ICP, used off-label. In more severe cases of IIH, where vision is threatened and there is a high risk of permanent blindness, surgical interventions are used initially followed by medication once ICP has been sufficiently lowered.

Medical options – currently no approved drug therapies in IIH

Despite insufficient evidence of efficacy, most patients are treated with Acetazolamide. The drug, marketed under the brand name of Diamox® and first introduced in 1960, is commonly used in glaucoma and is not well tolerated in patients with IIH, causing up to half of the IIH patients to discontinue their treatment

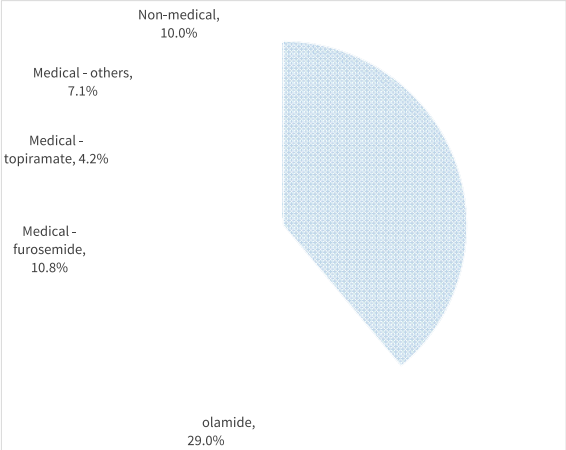
[5] The expanding burden of idiopathic intracranial hypertension: Mollan et al (2018)
6 https://www.mayoclinic.org/medical-professionals/ophthalmology/news/incidence-of-idiopathic-intracranial-hypertension-parallels-rising-rate-of-obesity/mac-20430150

making long-term management difficult. Other pharmaceutical-based treatments (Methazolamide, Furosemide, Topiramate) are also often used off-label for IIH but, as with Acetazolamide, have significant side effects with little evidence to support their use (Cochrane Review), and neurologists largely see them as ineffective.

Non-medical interventions[7] – surgical interventions for reducing CSF volume

In the subset of patients (around 10%) presenting with severe IIH with an imminent visual threat, it is urgent to identify and address with the right surgical intervention, either shunts, optic nerve fenestration (ONSF)[8] or venous stents. ONSF is typically offered as the first-line surgical treatment, with CSF shunting in second line when ONSF does not provide improvement. However, the failure rate with CSF shunting is high at over 50% and in a third of cases require multiple revisions. Occasionally, lumbar puncture is used to reduce ICP temporarily while awaiting surgery, or in pregnant patients who wish to avoid medical therapy.

Exhibit 5: Current therapeutic options for IIH – medical (drugs) + non-medical (surgery; other procedures)

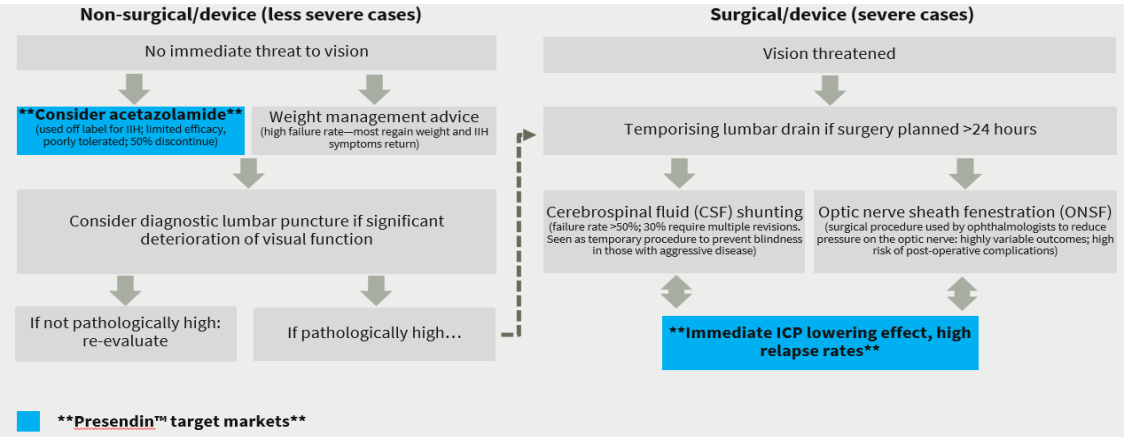


Source: Global Idiopathic Intracranial Hypertension Treatment Industry Market Research: Maia Research (2019); MST Access estimates.

Presendin™: Potential First Mover Advantage as Only Approved Drug for IIH

Given the lack of approved drug therapies and the shortcomings of currently used medications for chronic management of IIH, we see a role for Presendin™ in both less severe (milder) and severe cases of IIH in first-line settings and maintenance settings, respectively. This assumes Presendin™ meets clinical endpoints in the IIH EVOLVE trial and is ultimately approved for market release.

Exhibit 6: Treatment guidelines for IIH: current treatments are limited



Source: Invex Therapeutics.

[7] https://jnnp.bmj.com/content/87/9/982

[8] A surgical procedure performed to decompress the optic nerves by creating a window in the optic nerve sheath to release CSF from the subarachnoid space around the optic nerve

Clinical and Regulatory Strategy

Invex chose Exenatide, a synthetic form of exendin-4, as the preferred GLP-1 receptor agonist (GLP-1 RA) because of its breadth of available published safety data, its expiring patent status, and its fast onset of action. Presendin™ is the company's proprietary formulation of Exenatide, and is a once-per-week, subcutaneous, sustained release (SR) Exenatide microsphere formulation, originally developed by Peptron.

Invex has conducted preclinical studies and a single Phase 2 trial that met all key endpoints and has designed a global Phase 3 trial designed to meet regulatory requirements for approval in key markets worldwide. Presendin™ was awarded orphan drug designation in the EU and US for IIH in 2017. Invex's manufacturing and collaboration agreement with Korea-based Peptron, signed in September 2021, provides clinical synergies as well as manufacturing supply for trials.

Studies and Trials

Preclinical in-vitro and in-vivo studies (exendin-4): proof of concept

Preclinical research was conducted in 2019 by Dr Sinclair's group at the Institute of Metabolism and Systems Research, University of Birmingham, UK, using exendin-4.

Exendin-4 was evaluated in both in-vitro and in-vivo studies. Three experimental studies were performed (one in-vitro and two in-vivo).

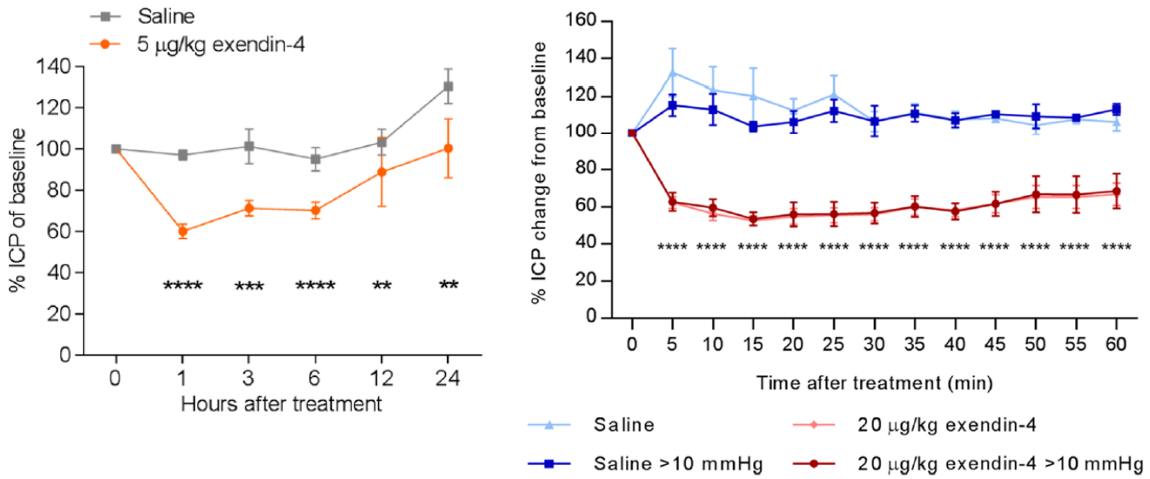
Design of studies:

- The in-vitro studies used tissue sections and choroid plexus epithelium cell cultures to assess the localisation and distribution of the GLP-1 receptors (GLP-1 Rs) in rat and human choroid plexus and determined the effects of GLP-1R stimulation on CSF secretion.
- The in-vivo studies investigated the effects of GLP-1 agonists on ICP in a hydrocephalus rat model with raised ICP.

Findings of preclinical studies – exendin-4 reduced ICP in rats, supporting the repurposing of GLP-1 RAs. The in-vivo and in-vitro results showed:

- the GLP-1R is expressed in the human choroid plexus
- exendin-4 acted via GLP-1R in the brain to reduce ICP in conscious rats
- ICP reduction was dose-dependent, with effects lasting for 24 hours (Exhibit 7).

Exhibit 7: Effects of exendin-4 in lowering ICP in healthy rat (left) and rat model of raised ICP (right)



Source: A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus: Botfield et al (2017).

Phase 2 trial of repurposed Exenatide (Presendin™) formulation meets all endpoints

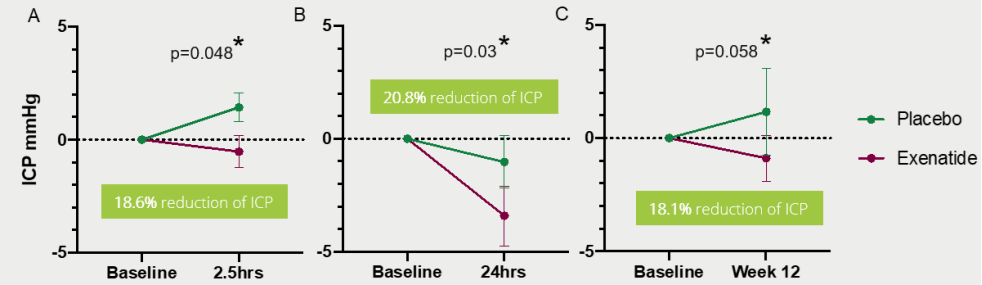
Design of trial: In 2019, Dr Sinclair was the principal investigator for the 16-patient Phase 2, double-blind clinical trial in female patients with IIH comparing subcutaneous 10mg Exenatide twice daily versus placebo.

Findings of clinical trial – support progressing to Phase 3 with statistically significant results: The primary endpoint of the study was the change in ICP over 12 weeks of dosing as measured by real-time patient monitoring devices. The trial, completed in May 2020, demonstrated a statistically significant reduction in key endpoints in the Exenatide arm, including all three primary endpoints related to ICP as well as in some key measures of clinical benefit. Statistically significant results were shown in:

- >10% reduction of ICP at 2.5 hours, 24 hours, and 12 weeks (Exhibit 8)
- 7.7-day reduction of monthly headache days (Exhibit 9)
- improvement in visual acuity (Exhibit 10).

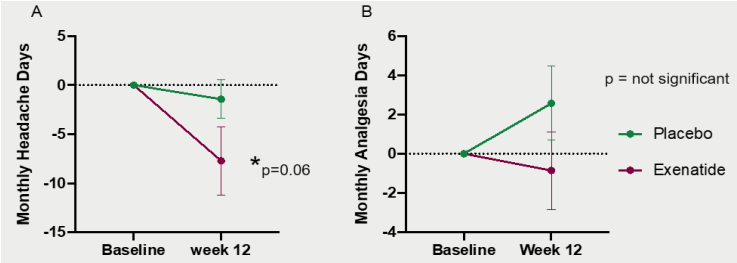
Importantly, the findings suggested benefits observed were not due to weight loss and showed low levels of adverse events, with nausea the most common. Based on the Phase 2 data Invex will now, subject to final ethics and regulatory approval, advance Presendin™ into a single Phase 3 registration study across approximately 37 centres in Europe, the UK, the US and Australia. The trial is designed to meet the requirements for regulatory approval in Europe, the UK and Australia.

Exhibit 8: Phase 2 results: primary endpoint – Exenatide reduces ICP in IIH patients



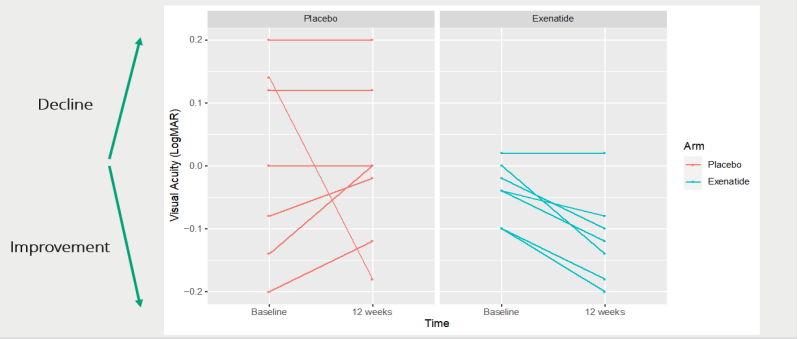
Source: Invex Therapeutics.

Exhibit 9: Phase 2 results: secondary endpoint – Exenatide reduces headache frequency



Source: Invex Therapeutics.

Exhibit 10: Phase 2 results: secondary endpoint – Exenatide improves visual acuity



Source: Invex Therapeutics.

Phase 3: Presendin™ entering pivotal clinical trial for EU, UK, Australia approval

Strategic rationale and design of trial: A single Phase 3 clinical trial (IIH EVOLVE) has been designed to meet the requirements for market approval of Presendin™ (sustained-release formulation of Exenatide[9]) for the treatment of IIH in the EU, UK, and Australia. The 240-patient trial will enrol newly diagnosed IIH patients across 37 centres in Europe, UK, Australia, and the US, with findings used to inform subsequent regulatory discussions with the FDA regarding the market approval of Presendin™ in the US. Recruitment is expected to take 24 months. Invex has lodged a Human Research Ethics Approval (HREC) application with a private hospital to commence IIH-EVOLVE patient recruitment in Australia in late 2021. The company plans to commence treatment of the first patient in late 1HCY22.

Patients will be randomised to receive either: (1) once weekly subcutaneous injections of Presendin™ or (2) a placebo.

Clinical trial endpoints: The primary endpoint of IIH EVOLVE will assess the mean difference in ICP from baseline at 24 weeks between the patients receiving Presendin™ vs. the placebo. Secondary endpoints will assess the relative difference in vision (measured by Perimetric Mean Deviation [PMD] and swelling of the optic disc [papilloedema] by optical coherence tomography [OCT]) and monthly headache days (MHDs) between the two groups over 24 weeks (see Exhibit 11).

Outcomes from the IIH EVOLVE clinical trial are expected to facilitate future discussion with the US FDA regarding registration in the US.

Exhibit 11: IIH EVOLVE trial design

Trial name	IIH EVOLVE – a Phase 3 clinical trial evaluating the safety and efficacy of Presendin™ in IIH.
Trial design	The trial is a randomised double-blinded, placebo-controlled, multi-centre clinical trial to determine the efficacy and safety of Presendin™ in IIH; ~37 centres planned to participate across Europe, the UK, the US and Australia; 240 patients with IIH to be randomised 1:1 versus placebo; patients self-medicate with either a once weekly PLGA* formulation of Exenatide (Presendin™) or placebo
Endpoints	
Primary endpoints	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 at baseline and at 24 weeks.
Secondary endpoints	To determine the effect of Presendin™ on changes in: (1) PMD – as measured by Humphrey Visual Field Analysis, (2) Papilloedema – utilising optical coherence tomography (OCT) to evaluate changes in optic nerve head size and retinal nerve fibre layer thickness, and (3) MHD – collected via an electronic patient diary over 24 weeks.
Safety endpoints	Adverse events rate, anti-drug antibodies, pharmacokinetics, and general lab measures
Quality of life	Patient reported outcomes (SF-36, ED-5D-5L, VFQ-25), monthly patient diary
Other details	
Start date	Late 1HCY22
Completion date (anticipated)	Recruitment anticipated to take up to 24 months followed by a 4 week safety follow-up
Sponsor	Invex Therapeutics
	*PLGA formulation: Presendin™ is a sustained release (SR) formulation of Exenatide in a biodegradable poly(lactic-co-glycolic acid) microsphere (PLGA)

Source: Invex Therapeutics.

Sequential regulatory strategy based on geography with all data informing US FDA regulatory requirements

Invex aims to gain a first-mover advantage in IIH with an optimised formulation of Exenatide. The Phase 3 IIH EVOLVE trial is specifically focused on meeting the requirements for registration of Presendin™ in the EU, the UK and Australia using a trial design based on advice received from the European Medicines Agency (EMA). Invex intends using the findings of the Phase 3 IIH EVOLVE clinical trial for Presendin™ to support an EMA (Europe), Medicines & Healthcare Products Regulatory Agency (MHRA – UK) and Therapeutic Goods Administration (TGA – Australia) approval for the treatment of IIH. As such, Invex aims to secure an early market approval for Presendin™ in the EU, UK, and Australia, and to use the data from IIH EVOLVE to further

[9] Sustained release formulation supports patient compliance and enhances clinical appeal of Presendin™

inform the interaction with the FDA and define fully the requirements for market approval of Presendin™ in the US.

Regulatory: Orphan Drug Designation Granted for IIH in Europe and US

Presendin™ was granted orphan drug designation in 2017 by the EMA (EU) and FDA (USA) for the treatment of IIH.

The Orphan Drug Designation Program was established in 1983 and provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders that

- affect fewer than 200,000 people in the US, or
- affect more than 200,000 people, but for which a manufacturer would not be expected to recover the costs of developing and marketing a treatment drug.

This means that if Presendin™ reaches the market before similar products, this could provide ten years and seven years of exclusivity from the date of approval in Europe and the US, respectively.

Collaboration and Manufacturing: Exclusive Agreement with Peptron

In September 2021, Invex announced that it had signed an exclusive long-term Collaboration and Manufacturing Agreement with Peptron, Inc. Pepton is a biopharmaceutical company based in Daejeon, Korea, which develops sustained-release peptide-based medicines.

The terms of the agreement

Presendin™ will be manufactured and supplied globally to Invex from Peptron's manufacturing facility in Osong, Korea, which can produce over 48,000 vials of Presendin™ per month, representing 12,000 IIH patient doses per month. Notably, this provides Invex with the ability to scale up rapidly to meet annual incidence.

Peptron has agreed to

- provide Invex with access to its intellectual property, including an extensive preclinical and clinical data package
- supply Invex with GMP-grade Presendin™ for all its clinical trials in IIH as well as for commercial use, once Presendin™ is approved.

Invex has agreed to

- pay a defined price per dose for the global supply of Presendin™ for clinical studies and for the first ten years following the first commercial sale
- grant Peptron an exclusive license to commercialise Presendin™ for IIH in Korea.

Benefits: significant clinical synergies for Exenatide formulation

Peptron has completed numerous preclinical and Phase 1 and 2 clinical trials in type 2 diabetes of polylactic-co-glycolic acid (PLGA[10]) formulations of Exenatide and is currently undertaking a Phase 2 trial in Parkinson's Disease. As such, we see significant synergies with Invex.

The deal with Peptron supports development of Presendin™ as a sustained release (SR) formulation of Exenatide in a biodegradable PLGA microsphere. This is the formulation used in the IIH EVOLVE trial. The benefit of this formulation is that it allows a once weekly injection format for patients with IIH, allowing for greater convenience and better compliance. PLGA is a well-established formulation solution approved by regulators including the US FDA for a variety of human diseases.

Presendin™ will be manufactured in Peptron's GMP facility in South Korea using Peptron's technology.

[10] Poly (lactic-co-glycolic acid) (PLGA) is the most widely used biomaterial for microencapsulation and prolonged delivery of therapeutic drugs, proteins and antigens. (https://www.frontiersin.org/articles/10.3389/fphar.2016.00185/full#B72)

Intellectual Property

Exenatide was originally approved in 2005 as Byetta® after it was co-developed by Amylin Pharmaceuticals and Eli Lilly and went generic in 2017.

Invex has established a comprehensive intellectual property portfolio that covers the use of its proprietary formulations of Exenatide, trademarked as Presendin™, in the modulation of CSF secretion.

Exhibit 12: Invex's patents related to elevated ICP treatment

Country	Application No.	Application Date	Status	Expiry Date
Europe	15757548.1	25/Aug/2015	Granted	n/a
Japan	2017-512008	25/Aug/2015	Granted	25/Aug/2035
USA	15/504,399	25/Aug/2015	Granted	25/Aug/2035
International	PCT/GB2015/052453	25/Aug/2015	Nationalised	

Source: Invex Therapeutics.

Exhibit 13: Trademarks for Presendin™ registered by Invex Therapeutics

Country	Application No.	Status	Next Renewal	HGF Ref.
Australia (International Designation)	1558488	Registered	21/Aug/2030	T296809WAU
Europe (International Designation)	1558488	Registered	21/Aug/2030	T296809WEP
International (Madrid Protocol)	1558488	Registered	21/Aug/2030	T296809WO
United Kingdom	UK00003462892	Registered	31/Jan/2030	T296809GB
USA (International Designation)	79297231	Registered		T296809WUS

Source: Invex Therapeutics.

Competitive Landscape

As previously noted, notwithstanding the common off-label use of Acetazolamide, Methazolamide, Furosemide and Topiramate in first line settings for less severe cases, there are currently no approved drugs available for the specific treatment of IIH. Further, there is little evidence according to the medical literature (Cochrane Review) to support the treatments that are currently used.

As such, we think Presendin™ is well positioned given its late stage of development and orphan drug designation, and absence of other product candidates in development according to clinicaltrials.gov, to gain a sustainable first-mover advantage pending the outcome of the IIH EVOLVE trial.

The only other drug in development previously targeting IIH is the selective 11β-HSD1 inhibitor AZD4017, a 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor. AZD4017 also targets the choroid plexus where it directly inhibits the activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme which regulates local steroid levels and mediates production of CSF.

AZD4017 completed a 31-patient Phase 2 trial (Clinicaltrials.gov ID NCT02017444) assessing the efficacy in lowering intracranial pressure in IIH; however, in results published[11] in January 2020, did not reach statistical significance. AZD4017 does not have an orphan drug designation and no further development of this drug has been undertaken based on database search.

[11] https://academic.oup.com/braincomms/article/2/1/fcz050/5699900#206518224

Financials

Invex listed on the ASX in 2019, raising $12m, and later added another A$26.2m (before costs) through a share placement in mid-2020. The company is essentially structured as a virtual business with a small number of key personnel based in the UK engaging additional expertise of clinical, regulatory, and manufacturing consultants as required. As such, costs are relatively low and largely driven by the funding of clinical development of Presendin™ which, subject to ethics approval, will commence a Phase 3 registration study in 1HCY22.

Invex reported a FY21 net loss after tax of A$2.284m, down 32% on the previous corresponding period's net loss of A$3.360m (which included a one-off impairment write down of A$0.118m and capital raising expenses of A$0.158m). This was largely due to the lower R&D costs of A$1.139m, versus A$1.591m in FY20, as a result of the additional time required to progress drug manufacturing to support commencement of the Phase 3 clinical trial. The loss included share-based payment expenses of A$0.562m, compared with A$0.983m in FY20.

Net loss for the six months ended 31 December 2021 was A$1.796m, compared with a net loss of A$1.056m in the prior corresponding period. The loss included share-based payments, costs associated with planning for the Phase 3 clinical trial, manufacturing of the drug, and the compliance and administration costs associated with Invex's status as an ASX-listed company.

Cash Position

The company remains in a strong financial position with cash at bank as at end of December 2021 of A$31.4m, down from A$32.7m as of 30 June 2021. According to management this should be sufficient to complete the Phase 3 pivotal study of Presendin™ in IIH for registration purposes across the major markets of the EU, UK and Australia. Cash burn in 2021 averaged around A$0.5m representing annualised corporate costs of ~A$1m per annum.

Research and Development

We expect R&D spend will increase significantly over the next 12 months as Presendin™ enters the 240-patient Phase 3 IIH-EVOLVE study and begins to enrol patients across 37 sites in Europe, UK, Australia, and the US. We assume R&D spend of A$24m over the next four years commencing 2022 comprising A$3m, A$5m, A$9m and A$7m, commensurate with the scale up of clinical trial sites across multiple jurisdictions and recruitment of trial patients.

Valuation

We value Invex Therapeutics at A$254m or A$3.38 per share on an undiluted basis, using a risk-adjusted net present value (rNPV) method to discount future cash flows through to 2035, consistent with the expiry of current patent families, shares on issue of 75,153,848 and including A$31.4m in cash as of 31 December 2021. There are currently 4,610,000 options outstanding, exercisable at various prices. As such, our fair value of the shares on a fully diluted basis is A$3.18 per share.

Our valuation assumes a go-it-alone strategy with gross margins upon launch of 55% representing underlying gross margin of 85% with costs (R&D, launch and marketing) paid by Invex Therapeutics less an average margin for third-party distribution of 30%.

We assume R&D spend of A$24m over the next four years commencing 2022 comprising A$3m, A$5m, A$9m and A$7m commensurate with the scale up of clinical trial sites across multiple jurisdictions and recruitment of trial patients. Given the strategy of prioritising regulatory approvals, we assume launch in Europe and the UK in 2025 followed by a US launch in 2028.

The breakdown of our rNPV model, which includes A$31.4m in cash as reported at end of December 2021, a probability of success given phase of clinical development and using a 12.5% discount rate, is shown in Exhibit 14.

Exhibit 14: rNPV-based valuation model

Product	Indication	Launch	Peak sales (US$m)	NPV*(US$m)	Probability of success	rNPV (A$)
Presendin™	Idiopathic Intracranial Hypertension	Europe/UK in 2025 - United States in 2028	396	282	50%	222,828,649
Net cash (31 Dec 2021)						31,366,041
Shares outstanding						75,153,848
rNPV/share						3.38
*Assumes go-it-alone strategy						

Source: MST Access.

Notwithstanding multiple clinical indications involving raised ICP, and management's flagging of the commencement of a Phase 2 study in a second indication, Invex's main value driver at this point is the progress of Presendin™ towards approval in IIH. Further, consistent with its stated clinical strategy, we assume launch in Europe and the UK pending positive readout of the IHH EVOLVE trial to occur in 2025, and similarly pending FDA approval in 2028 in the United States.

Exhibit 15: Valuation – key assumptions

Asset/indication	Metrics	Assumptions
Presendin™		
Idiopathic Intracranial Hypertension	Target population	**Europe/UK population of ~ 516m.** Assumes incidence of 4.7 patients per 100,000 population with average treatmer period of 4.3 years. Growth in incidence of 3.4% per annum given correlation with obesity, with 60% diagnosed of which 90% are treatable with drugs.
	Pricing*	US$1,500 per month which equates to 75% of US pricing (See below) , given historical precedents. Assuming a go-it-alone strategy with third party distributors in different markets generating a gross margin of 55%.
	Trial timelines	Assuming completion of IIH EVOLVE phase 3 trial over three years with launch in 2025 In Europe/UK.
Presendin™		
Idiopathic Intracranial Hypertension	Target population	**United States population of ~ 332m.** Assumes incidence of 4.7 patients per 100,000 population with average treatment period of 4.3 years. Growth in incidence of 3.4% per annum given correlation with obesity, with 60% diagnosed of which 90% are treatable with drugs.
	Pricing*	**US$2,000 per month**; This assumes Presendin™ is priced at a 3 times multiple, given Orphan Drug premium, to a blend of Byetta® and Bydureon® in type 2 diabetes (One month of Byetta® of US$700 Versus one month of Bydureon of US$660). Assuming a go-it-alone strategy with third party distributors generating a gross margin of 55%.
	Trial timelines	Assumes launch into the US market in 2028

*www.goodrx.com/conditions/diabetes-type-2/byetta-vs-bydureon-whats-the-difference

Source: MST Access.

Sensitivity Analysis – Varying Pricing and Market Penetration

We regard pricing and market penetration as key drivers of our valuation at this stage. As such, we provide a sensitivity matrix to highlight the impact to our valuation of both these key metrics (see Exhibit 16).

Our base-case valuation of A$3.38 per share (undiluted) incorporates a reference price of US$2,000 per month and assumes peak market penetration of 25% in Europe and the UK by year 4 post launch in 2025.

We have used published pricing for Byetta® and Bydureon® in type 2 diabetes to benchmark our price point and a three-times multiple[12] to reflect the fact that Presendin™ will potentially be the first approved, albeit repurposed, drug in this rare disease indication and with an Orphan Drug Designation.

In all scenarios, our assumptions around market penetration in the US post launch in 2028 remain static at 10%, 20% and 25% in years 1, year 2 and year 3 respectively. We see the market exclusivity afforded by the Orphan Drug Designation in both Europe and the US as supporting peak market penetration up to the end of the drug patent's life in 2035.

Exhibit 16: Sensitivity matrix: impact of pricing and market penetration on Invex Therapeutic valuation

Reference* pricing per month (US$)	Peak market penetration within 4 years of launch (Europe/UK)					
3.38	15.0%	20.0%	25.0%	30.0%	35.0%	40.0%
1600	1.82	2.22	2.62	3.02	3.42	3.82
1800	2.10	2.55	3.00	3.45	3.90	4.35
2000	2.38	2.88	3.38	3.88	4.38	4.88
2200	2.67	3.22	3.76	4.31	4.86	5.41
2400	2.95	3.55	4.15	4.75	5.35	5.95
2600	3.23	3.88	4.53	5.18	5.83	6.48

Source: MST Access. *Pricing benchmarked to a blend of Byetta® and Bydureon® in type 2 diabetes (One month of Byetta® of US$700 versus one month of Bydureon® of US$660) and using a three time multiple. - www.goodrx.com/conditions/diabetes-type-2/byetta-vs-bydureon-whats-the-difference

[12] "What price do we pay for repurposing drugs for rare diseases"? Simoens et al (2016)

Sensitivities and Risks

Drug repurposing – identifying and developing new uses for existing drugs – is a well-established and relatively lower-risk approach to drug development. By pursuing reformulation rather than undertaking drug discovery, companies can significantly shorten the timelines required to develop a drug and usually lower the associated costs. However, despite Exenatide's orphan drug designation status, late-stage development phase and attractive market opportunity, Invex's single drug development program focus exposes investors to several key risks, both company-specific and relating to the biotech sector in general.

New Drugs in Development, Generic Competition, and Intellectual Property

Although it is important to consider potential competition from new treatments, drug development programs targeting IIH at present are sparse, according to clinicaltrials.gov. Further, current formulations of exenatide on the market are neither approved nor optimised for use in IIH. As such, we see the risk of substitution with current formulations as minimal. These could include generic versions of Bydureon®[13] (Exenatide) that may be developed for use in type 2 diabetes which would still have issues associated with either under or overdosing given the lack of safety data in IIH. Direct generic competition to Presendin™ through a paragraph IV challenge[14] remains a possibility. However, this risk is mitigated by Presendin™'s orphan drug designation, which should (subject to the drug's approval) provide 10 years and 7 years market exclusivity for Europe and the USA, respectively. Patents currently extending to August 2035 also provide another barrier to potential rivals.

Clinical Risk and Specific Development Risk Associated with Formulation

Although Exenatide is already approved for therapeutic use in humans by the European Medicines Agency (EMA) and the US FDA for the treatment of type 2 diabetes, there is no guarantee that a reformulated Exenatide such as Presendin™ will receive regulatory approval. Further, clinical trials can be delayed or fail to demonstrate any benefit, or research may cease to be viable for a range of scientific, regulatory, and/or commercial reasons. Although clinical readouts to date have been positive there is still a risk that the Phase 3 IIH EVOLVE trial does not meet its primary endpoints.

Limited Company History

Invex was founded to advance a specific area of research and has a relatively short history as a company. Transitioning to a fully-fledged biopharmaceutical company will require additional resources and access to specialised skill sets.

Commercial Execution

Notwithstanding achieving technical and regulatory approvals, the company will need to secure an appropriate licensing deal or achieving an alternative means of commercialising Presendin™. The agreement with Peptron lowers this risk at the manufacturing and product supply levels, but uncertainties remain around end-market distribution. That said, management has indicated a preference for crystallising shareholder value through a transaction for the entire company.

Risk of Additional Funding Requirements – Funded through to Registration

A successful share placement raising $26.2m in June 2020 means Invex is fully funded to proceed with its Phase 3 clinical trial of its proprietary Presendin™ formulation of Exenatide. However, cost of trials and operational expenses may overrun estimates and require additional capital to be raised.

Reliance on Key Personnel

The company depends on the principal members of its scientific and development team, the loss of whose services could materially adversely affect Invex and impede the achievement of its research and development objectives.

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[13] In 2014, AstraZeneca received FDA approval for Bydureon® (exenatide extended-release for injectable suspension) 2mg, the first once-weekly medicine for adults with type 2 diabetes. As such, it is well characterised with a well-established safety profile. Exenatide has not yet been approved for any other indication.

[14] A company can seek FDA approval to market a generic drug before the expiration of patents related to the brand-name drug that the generic seeks to copy.

Board and Management

Dr Jason Loveridge – Non-Executive Chairman. Dr Loveridge is a founder of Invex Therapeutics and is CEO of 4SC AG, a German-listed oncology company. He has more than 30 years of international experience across Europe, Asia and the US in senior management positions in life sciences companies and as an investment professional dealing in both privately held and publicly traded companies. Additionally, he has substantial transactional experience in the sale and partnering of biotechnology assets. Dr Loveridge graduated in Biochemistry and Microbiology from the University of New South Wales, Australia, and holds a PhD in Biochemistry from the University of Adelaide, Australia. He is a fellow of the Royal Society of Medicine.

Prof Alexandra Sinclair – Executive Director and Chief Scientific Officer. Prof Sinclair is a founder of Invex Therapeutics and a Clinician Scientist and Neurology Consultant in the Metabolic Neurology Group at the Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, The University of Birmingham, UK. She runs the Headache Service and Idiopathic Intracranial Hypertension Service at University Hospital Foundation Trust.

Prof Sinclair is a member of the British Medical Association and the Association of British Neurologists (ABN) and is a Fellow of the Royal College of Physicians, London. She is a member of the board for the European Headache Federation and is on the scientific committees for the North American Neuro-Ophthalmology Society (NANOS). She is also a council member for the British Association for the Study of Headache (BASH). Prof Sinclair is on the MRC Neuroscience and Mental Health Board and the Midland Neuroscience Teaching and Research Fund Board, as well as being Chair of the Brain Research UK Scientific Advisory Board. Previously, she was an elected board member of the IHS and was the Deputy Chair for the Association for British Neurologists grouping for Headache and Pain (ABN AAG). She was previously on the research committee for the Association for British Neurologists and was also the patron of the patient charity IIH UK.

Dr Tom Duthy – Executive Director. Dr Duthy has over 15 years of financial markets experience in sell-side equity research and senior executive roles across investor relations (IR) and corporate development. He is Founder and CEO of Nemean Group, a boutique corporate advisory and IR firm which delivers value-added services across the life sciences, medical devices, healthcare, technology, and emerging company sectors. Prior to establishing Nemean in October 2018, Dr Duthy was Global Head of Investor Relations & Corporate Development at Sirtex Medical (ASX: SRX), which was sold to CDH Investments in September 2018 for A$1.9 bn (the largest medical device transaction in Australian corporate history). Previously, he spent 10 years as a leading sell-side Healthcare & Biotech analyst at Taylor Collison, focused mainly on small caps, during which time ~$200m in equity capital was raised for selected portfolio companies. He is a Member of the Australian Institute of Company Directors (MAICD) and the Australasian Investor Relations Association (AIRA).

Mr David McAuliffe – Non-Executive Director. Mr McAuliffe is an experienced entrepreneur and board director with over 20 years' experience in the international biotechnology field. He has been involved in numerous capital raisings and in-licensing of technologies. He has founded several companies in Australia, France and the UK, many of which have gone public. Mr McAuliffe has an Honours degree in Law, a Bachelor of Pharmacy degree and is President of Dyslexia – Speld Foundation WA. He is a director of 4DS Memory Ltd.

Ms Narelle Warren – CFO and Company Secretary. Ms Warren is a Chartered Accountant with over 20 years of corporate advisory, financial management and company secretarial experience. She has coordinated and assisted in a number of corporate transactions, including acquisitions, divestments and raising funds via private and public equity markets. Ms Warren holds both a Bachelor of Laws and Bachelor of Commerce.

Dr Megan Baldwin – Non-Executive Director. Dr Baldwin is CEO and Managing Director of Opthea (ASX:OPT; NASDAQ:OPT), a late-stage biopharmaceutical company developing a novel therapy to address unmet need in the treatment of retinal eye diseases, including wet age-related macular degeneration (wet AMD). Under Dr Baldwin's leadership, Opthea has rapidly advanced its ophthalmology program through Phase 1–2 clinical development, was added to the S&P/ASX 300 in June 2020 and in October 2020 completed a $180m IPO and listing on the US NASDAQ to progress two pivotal Phase 3 studies in wet AMD. Dr Baldwin is an experienced biotechnology executive with over 20 years' experience working on therapeutic drug development programs for cancer and ophthalmic indications. She was previously employed at Genentech (now Roche) as a postdoctoral researcher before moving to Genentech's commercial division. She also serves on the Board of Ausbiotech as Deputy Chair.

Appendix 1 – Shareholder Registry

Exhibit 17: Top 20 shareholders (as at 1 January 2022)

Ordinary Shareholders	Number	Percentage
Tattarang	8,846,154	11.77
Tisia Nominees Pty LTd <Henderson Family A/C>	4,000,000	5.32
Dr Jason Loveridge	3,374,462	4.49
Mr David Jerimiah McAuliffe	3,350,001	4.46
Anthony Grist	3,000,000	3.99
JK Nominees Pty Ltd < The JK A/C>	3,000,000	3.99
Alexandra Jean Sinclair	2,500,000	3.33
Mrs Kathryn Salkiild	2,293,000	3.05
The University of Birmingham	2,000,000	2.66
Bannaby Investments Pty Ltd <Bannaby Super Fund A/C>	1,625,000	2.16
Sunset Capital Management Pty Ltd <Sunset Superfund A/C>	1,448,175	1.93
Citicorp Nominees Pty Ltd	1,361,383	1.81
Cityscape Asset Pty Ltd <Cityscape Family A/C>	1,250,000	1.66
Cabletime Pty Ltd	1,120,000	1.49
Sandhurst Trustees Ltd <Collins St Value Fund A/C>	1,081,924	1.44
JP Morgan Nominees Australia Pty Ltd	730,000	0.97
Netwealth Investments Ltd	663,751	0.88
Peter Kyros Pty Ltd <Kyros SF A/C>	583,616	0.78
Palla Nominees Pty Ltd < P C Blackman S/F No2 A/C>	580,000	0.77
HSBC Custody Nominees (Australia) Limited	563,184	0.75
Top 20 total	43,370,650	57.70
Total remaining holders balance	31,783,198	42.30
Total	75,153,848	100.00

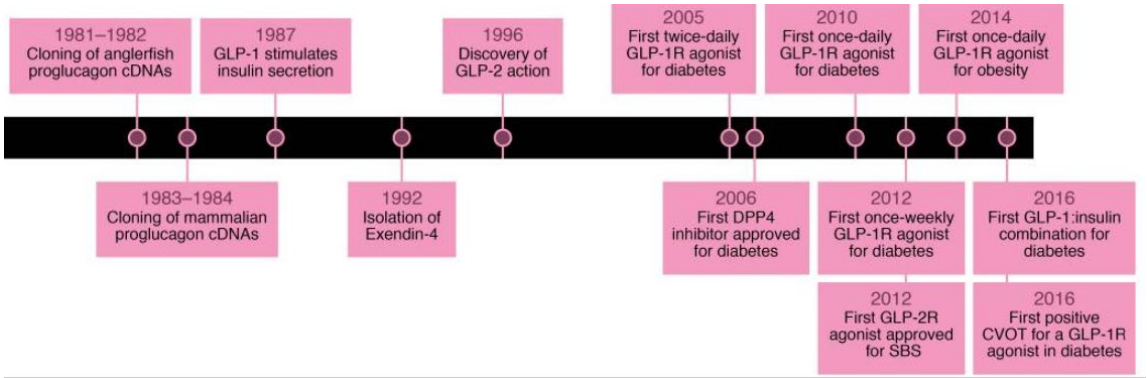
Source: Invex Therapeutics.

Appendix 2 – Clinical Development of GLP-1 Peptide Therapeutics

History of Clinical Development of GLP-1 Peptide Therapeutics Underpins Safety Profile

Development of GLP-1 peptide therapeutics commenced in the early 1980s and was first approved for treatment of patients with type 2 diabetes. The mechanism of action in diabetes relies on the ability of GLP-1 agonists to stimulate insulin and inhibit glucagon secretion, coupled with inhibitory effects on food intake and gastric emptying. Although this mechanism of action differs from Presendin™'s targeting of GLP-1 receptors in the choroid plexus, we think the long history of clinical development underpins a well understood safety profile.

Exhibit 18: History of GLP-1 agonist therapeutics



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707151/

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