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Update on IIH EVOLVE Phase III Clinical Trial & Initiation of an Independent IIH Market Assessment

Key Points:

- **Lower than expected enrolment trajectory for IIH EVOLVE Phase III trial, due to higher screening failures and slower site activations than expected**
- **Revisions to Phase III clinical trial design required to remedy current design bottlenecks to enrolment**
- **Invex to focus on improving patient enrolment with amendments to both key inclusion criteria and secondary endpoints**
- **In parallel, the Company will complete a detailed market assessment initiated to understand the risk of approved GLP-1 receptor agonists to Invex's IIH market opportunity**
- **Anticipated cash balance to 30 June 2023 of approximately $22.6 million**

Invex Therapeutics Ltd (**Invex**, **ASX:IXC,** or **the Company**) a clinical-stage biopharmaceutical company focused on the development and commercialisation of Presendin™ (sustained release Exenatide) for neurological conditions relating to raised intracranial pressure, today provides an update on the progress of the IIH EVOLVE Phase III clinical trial for patients with Idiopathic Intracranial Hypertension (IIH).

The Company has undertaken a strategic evaluation of its Phase IIH EVOLVE program investigating Presendin™, a GLP-1 receptor agonist (GLP-1RA), in response to the slower than expected site activations and patient enrolment into the IIH EVOLVE Phase III clinical trial and the rapidly evolving market uptake of GLP-1RAs for the treatment of obesity with or without co-morbidities such as type II diabetes.

IIH EVOLVE Site Activation and Recruitment

For IIH EVOLVE, the Company was targeting a total of 240 patients with newly diagnosed IIH for enrolment into the trial, with recruitment expected to take up to 24 months. The trial recruited its first patient in November 2022 in Adelaide, Australia.

The slower than anticipated recruitment and delay in site activations has impacted Company timelines on recruitment into the IIH EVOLVE trial. As at 26 June 2023, the Company has enrolled 13 patients into the IIH EVOLVE trial with a total of 12 sites activated out of the target sites of 40 globally, which is behind expectations. A total of 25 patients with IIH have been screened for

potential enrolment into the trial, with the Company noting a significantly higher failure rate than initially anticipated, albeit from a limited number of activated sites, as discussed below. In addition, based on data collected from the enrolling sites, over 50 additional IIH patients have been pre-screened and not progressed to screening predominately due to their diagnostic lumbar puncture being outside of the time threshold of 4 weeks or less for formal screening.

The Company had targeted the majority of clinical sites (n=40) to be activated and open to enrol patients by 30 June 2023. To date, the Company has completed the necessary contracting and commenced site activations within Australia, New Zealand, the United States (US) and the United Kingdom (UK). However, the process of opening the 39 selected sites thus far who have been qualified by Invex to recruit patients has been slower than anticipated. The rate of site activations has also been impacted by the time taken to obtain the necessary regulatory approvals from Germany (20 March 2023), Israel (20 April 2023) and France (21 April 2023).

The Company has undertaken an analysis of screen failures with sites activated to date, which has identified a significant barrier to recruitment of an IIH patient into the trial; namely the Perimetric Mean Deviation (PMD) score between -2 to -7 decibels (dB) in at least one eye. Invex's analysis has found approximately 60% of IIH patients screened to date have recorded a PMD score outside of the inclusion criteria and were therefore ineligible for the trial (screen failures). PMD provides a measure of the total amount of visual field loss in patients.

As part of the trial design, Invex is seeking a clinically significant improvement in PMD as one of a number of secondary endpoints, alongside a reduction of intracranial pressure (ICP) as the primary endpoint of the study. The Company has statistically powered the IIH EVOLVE trial to achieve both ICP and a number of secondary endpoints, including PMD, consistent with regulatory feedback from the European Medicines Agency (EMA) and protocol assistance received in June 2021 from the US Food and Drug Administration (FDA).

In light of the recruitment rate and site activations described above, Invex has elected to withdraw guidance relating to the expected recruitment of the IIH EVOLVE trial, which was anticipated at take approximately 24 months from commencement of patient recruitment in Q4 CY2022.

IIH EVOLVE Phase III Initial Proposed Changes (Subject to Regulatory and Ethics Approval)

The Board, having consulted extensively with its regulatory and clinical experts, has decided to significantly amend the current protocol for the IIH EVOLVE trial and will actively seek the requisite authorities' feedback and ethics committee approvals for a revised protocol.

The Company intends to make several important changes to the study protocol. The primary endpoint will remain unchanged, with Invex assessing the change in ICP from baseline at 24 weeks in the Presendin™ arm versus placebo in newly diagnosed IIH patients who have received a diagnostic lumbar puncture within 6 months of enrolment into the trial (previously 4 weeks). The protocol changes will focus on reordering of the secondary endpoints by replacing PMD as the key secondary endpoint with the more robust Quality of Life Short form 36 (SF-36) Physical component score (PCS). SF-36 PCS is evidenced in IIH[1] and has been examined in several major IIH trials[2,3]. The EMA rates quality of life measures highly when examining market authorisations in Europe.

As a result of these changes, the sample size required to provide sufficient statistical power to detect a statistically significant and clinically meaningful effect in both ICP and SF-36 is 130 patients. The original IIH EVOLVE trial protocol required 240 patients. In addition, the proposed amendments to the protocol will include a six month open label extension for IIH patients in which all patients will received Presendin™, to gather additional safety data and to encourage participation in the trial.

Overall, the changes are expected to be cash neutral with respect to the original IIH EVOLVE trial costing, with recruitment anticipated to materially accelerate due to an expected significant reduction in pre-screen and screen failures.

The Emerging Use of GLP-1 Receptor Agonists (GLP-1RA) in Obesity Management

Invex has been closely monitoring the use of approved GLP-1 receptor agonists (GLP-1RA), specifically semaglutide, currently sold under the brand names Ozempic®, Wegovy® and Rybelsus®. Semaglutide has been shown to reduce body weight by approximately 15% in well-controlled studies of overweight patients with a Body Mass Index (BMI) of >30.[4] Pre-clinical data supported the preferential use of Exenatide for IIH due to its superior and rapid ICP lowering effects in animal models compared to other GLP-1RA, which Invex then demonstrated clinically in the Phase II PRESSURE study that reported in May 2020.

In Europe and the US, Wegovy® is approved for adult patients with obesity (BMI>30) or for overweight adults (BMI>27<30) who have at least one weight-related condition (such as high blood pressure, type 2 diabetes, or high cholesterol). In Europe and the US, Ozempic® is approved for the treatment of adults with insufficiently controlled type 2 diabetes as an adjunct to diet and exercise. In IIH, approximately 14% of patients are hypertensive and a minority of patients (~5%) have type 2 diabetes.[5]

Based on screening data and feedback from participating clinicians, Invex believes only a small percentage of IIH patients (<5%) considered for IIH EVOLVE have not elected to participate in the trial due to their desire to seek direct treatment with semaglutide. However, over time the increasing availability of these drugs may impact the execution of the IIH EVOLVE Phase III clinical trial as patients potentially elect to not participate in the study due to a 50% chance of receiving placebo initially for 24 weeks. Availability of the approved GLP-1RAs in Europe has been limited to date, due to manufacturing constraints and a materially lower price point compared to the US market, but this is expected to normalise over time.

The link between obesity and IIH is well established. Patients with IIH are typically female, and more than 90% of these sufferers are obese. IIH incidence is increasing in line with the increasing incidence of obesity, with the incidence of IIH approaching 20 per 100,000 of population in the obese population, with up to 64 per 100,000 in females. [6,7,8]

Invex considers the use of these agents in the management of obesity particularly as a key potential future risk to the acceptability of Presendin™ as an orphan treatment in IIH.

Accordingly, the Company has engaged a specialised global healthcare intelligence group to undertake an analysis on the potential future risks to the addressable market for Presendin™ for IIH. The results of the analysis will be available in mid Q3 CY2023. The Board will then be in a position

to fully assess the market opportunity for Presendin™ in IIH in light of new GLP-1RAs including Ozempic® and Wegovy® and whether to continue with the revised protocol change for the IIH EVOLVE Phase III clinical trial.

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This release dated 28 June 2023 has been authorised for lodgement to ASX by the Board of Directors of Invex Therapeutics.

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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. 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 Presendin™

Presendin™ is a once per week, sub-cutaneous, sustained-release (SR) Exenatide microsphere formulation originally developed by Peptron, Inc. (KOSDAQ: 087010). In September 2021 Invex entered into an exclusive collaboration, manufacturing and supply agreement with Peptron for Presendin™ in IIH for all major markets, with the exception of South Korea.

Exenatide is a small peptide and a synthetic version of the GLP-1 agonist exendin-4, which is currently approved for the treatment of type 2 diabetes. In 2017, Invex received orphan drug

designation for Exenatide in IIH from the US Food and Drug Administration and European Medicines Agency.

About the IIH EVOLVE Clinical Trial

The Phase III IIH EVOLVE trial is a randomised, placebo-controlled, double-blind, multi-centre trial that will randomise 240 patients with newly diagnosed IIH to determine the efficacy and safety of Presendin™ versus placebo, administered once weekly. Patients with a confirmed diagnosis of IIH will be randomised on a 1:1 basis to either Presendin™ or placebo for 24 weeks.

The primary endpoint of the trial is the change in intracranial pressure (ICP), as measured by lumbar puncture, at baseline and at 24 weeks. Secondary endpoints include the change in perimetric mean deviation (PMD), papilloedema and monthly headache days over 24 weeks.

IIH EVOLVE is designed to meet the requirements for market approval of Presendin™ for the treatment of Idiopathic Intracranial Hypertension (IIH) in the European Union (EU), United Kingdom (UK) and Australia.

Further study details can be found at clinicaltrials.gov website under Identifier **NCT05347147** or by visiting: https://clinicaltrials.gov/ct2/show/NCT05347147.

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