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Proprietary IHL-216A for Concussion/Traumatic Brain Injury ('TBI') and CTE

A potential Candidate for FDA 505 (b)(2) Accelerated Drug Approval, *submission to be made subject to successful clinical assessments*

Expert Opinion from Camargo Pharmaceutical Services and Dr Sud Agarwal

Independent Strategic Assessment Report

- IHL commissioned Camargo Pharmaceuticals Services ('Camargo') to provide an independent strategic assessment report on the FDA approval pathway for cannabinoid IHL-216A for the treatment of secondary brain injuries associated with TBI and concussion
- Camargo is an expert FDA advisory having advised upon more than 250 successful FDA applications over 17 years
- Camargo affirmed ability to make 505(b)(2) FDA submission for IHL-216A, reducing time and cost to commercialisation, subject to successful clinical assessment
- Plan to bring a registered drug to prescription market within 3 years; potential for unregistered sales sooner
- TBI is a serious and life-threating condition over which IHL-216A addresses an unmet medical need, facilitating a potential pathway for FDA expedited review programs

IHL-216A – intended to be a first in line defence against head trauma globally

- IHL-216A is being assessed for its ability to protect the brain against the injury mechanisms that cause cell death and other negative consequences in the weeks and months following all incidences of head trauma
- TBI accounts for approximately 10 million deaths and/or hospitalisations annually in the world (Schuman et al., 2017)
- There are currently no FDA/TGA approved pharmaceutical agents (drugs) approved for its treatment
- Most common events causing TBI include:
  - Falls from ladders or down stairs
  - Vehicle related collisions (drivers, pedestrians and cyclists)
  - Sports injuries
  - Violence and crime
  - Combat injuries

IHL-216 designed to ablate secondary brain injuries that lead to neurological deficits

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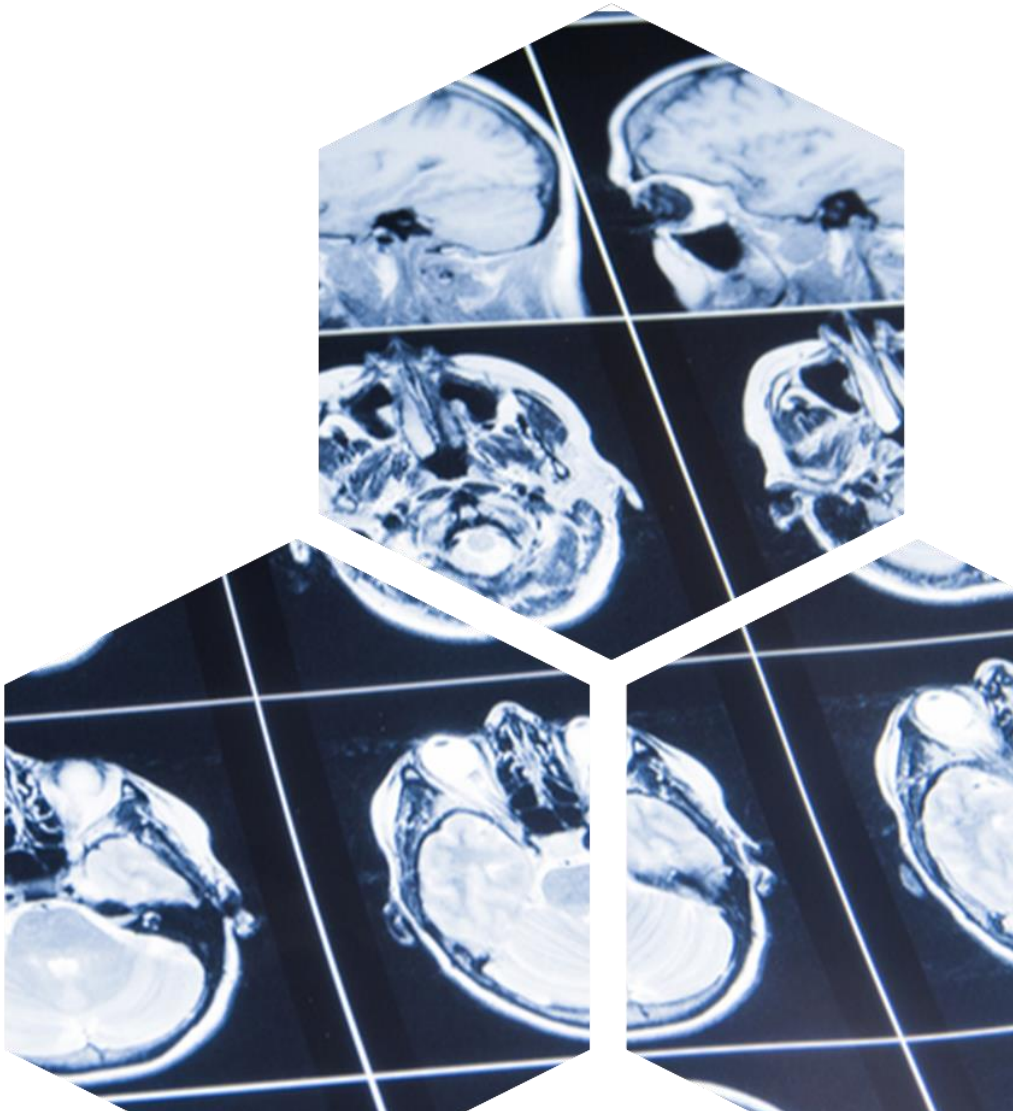
- Primary injury events encompass the mechanical damage that occur at the time of trauma
- Secondary brain injuries evolve over minutes, days and even months after the primary insult and result from biochemical, metabolic and cellular changes initiated by the primary event
- Secondary injury cascades are thought to account for the development of many of the neurological deficits observed after TBI, and their delayed nature suggests that there is a therapeutic window for treatment to prevent progressive tissue damage and improve patient outcomes (Loane and Faden, 2010).
- IHL-216A theorised to be administered in the immediate period after primary injury to prevent development of brain injuries
- Ablating secondary TBI injuries potentially has positive ramifications for long term conditions, including chronic traumatic encephalopathy (‘CTE’), a major health risk associated with contact sports e.g. MMA, NFL, AFL and NRL.



Neurological deficits associated with TBI and concussion

- There are many debilitating problems resulting from TBI and concussion:
  - Cognitive; memory, learning, reasoning, judgement, attention-span
  - Executive functioning; planning, decision making, multi-tasking, problem solving
  - Social; conversational difficulties, confusion
  - Behavioural; self control, risky behaviour
  - Emotional; anxiety, depression, moodiness, anger, insomnia
  - Sensory; dizziness, ringing in ears, impaired vision, impaired smell, poor hand-to-eye coordination
- Degenerative brain diseases; dementia and CTE (associated with contact sports)
- Post concussion syndrome
- Post traumatic epilepsy
- Headaches and nausea
- Vertigo

IHL-216A Indicative Clinical Program

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Q2 CY202O - Animal Studies

4-arm animal study in rodents following induced head trauma

Q3 CY2020 – Phase 2b Clinical Trial

Study in up to 50 MMA fighters to commence once COVID-19 related restrictions have been relaxed*

Q1 CY2021 – Phase 2 Dose Finding Study

Optimal dose finding study

CY2022 – Phase 3 Clinical Trial

- Animal studies to provide important data and will investigate synergistic action between cannabidiol ('CBD') and halogenated volatile anaesthetic agents
- CBD, under the brand name Epidiolex, has been registered for Dravet syndrome and halogenated volatile anaesthetic agents have been approved for use by FDA, facilitating IHL's decision to utilise the 505(b)(2) accelerated FDA New Drug Approval program
- IHL anticipates that Phase 1 clinical trials will only be required should the Phase 2b clinical trial find that API dosages in IHL-216A should exceed dosages observed in existing publicly available data recognised by the FDA

**Note: COVID-19 social distancing regulations have delayed the expected time to commence the phase 2b clinical assessment. The Company wishes to outline that social distancing measures are not expected to delay the clinical assessment of IHL-42X for OSA because the initial phase 2b clinical trial is undertaken using polysomnography equipment trial participants can use at home.*

IHL-216A Animal Studies

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- 4-arm study in 60 rodents
- Undertaken to confirm existing understanding of secondary injury mechanisms
- Superior results in combination of CBD and halogenated volatile anaesthetic agents would provide 'proof of concept' and will confirm the provisional patent, facilitating procession to patent application
- Animal studies provide important supportive data, from behavioural tests, magnetic resonance imaging and biomarkers associated with secondary injury cascades postmortem

Study Outline

Project Title	**Efficacy Evaluation of a Combined Therapy in CCI Rat TBI Model**	
Compliance	Non-GLP	
Test articles	CBD and isoflurane [IHL-216A]	
Vehicle	N/A	
Controls	Negative: placebo Positive: N/A	
Research System	**Species**	SD rats
	Gender	24 male and 24 female
	Age	10-week-old, 220-250 g
	Number	60 in total (12 for backup)

Group	Treatment	Route of Admin.	Frequency	Animals	
				F	M
1	Placebo/Placebo	Inhaled	BID, for 7 days; 1st dose at 15-30 minutes post injury	6	6
2	CBD/Placebo			6	6
3	Placebo/Isoflurane			6	6
4	CBD/Isoflurane			6	6

Assessments	
General observations	- Clinical signs, adverse reactions, mortality, etc.: Daily - Body weight: 2x weekly
Behaviour tests	- Morris water maze: 5 days training and tests on Day 7 - Elevated plus-maze: Day 3 and Day 7 - Motor: Rotarod test: Day 3 and Day 7
Imaging	- MRI: Day 7
Biomarker	- Immunofluorescence: GFAP, TNF-α, UCH-L1, Il-1β

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Phase 2b Clinical Trial in MMA Fighters

- Clinical trial participants are MMA fighters who receive head knocks and show symptoms of TBI and concussion
- Trial will investigate neurocognitive function in up to 50 participants that have sustained a concussion, comparing those that receive IHL-216A to those that receive a placebo
- Concussions will be diagnosed and ranked with the aid of the FitGuard concussive measuring smart mouthguard and FDA recognised neurocognitive and neuroradiological tests
- Neurocognitive tests cover aspects of cognition including attention, memory, language, reaction time and perception. Each fighter will complete baseline neurocognitive tests that will be repeated at various junctures post trauma to compare the IHL-216A and placebo cohorts
- Along with measuring duration to recovery (“return to play”), endpoints will include an array of brain-injury related blood biomarkers

Unregistered Sales Prior to Registration

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- Sales achievable prior to FDA registration and after clinical justification following initial Phase 2b clinical trial, subject to clinical success
- Unregistered sales may be achievable the via Special Access Scheme (‘SAS’) in Australia and through dispensaries in United States, Canada and other jurisdictions
- The SAS is a TGA pathway available to access 'unapproved' therapeutic goods. The application requires a clinical justification for the use of the product.
- Registration will facilitate prescription by all doctors, physician marketing and access of public reimbursement bodies, e.g. PBS in Australia
- IHL-216A is designed to satisfy World Antidoping Authority (‘WADA’) and Australian Anti-Doping Authority’s (‘ASADA’) specifications for use by elite athletes at risk of TBI and CTE

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'Expedited Review Programs' – Camargo Expert Advice

- TBI is a serious and life-threating condition over which IHL-216A addresses an unmet medical need
- There is no pharmaceutical (drug) treatment approved for TBI in any jurisdiction. Current treatment for severe TBI includes decompressive craniotomy, a highly-invasive procedure to drill into the skull to drain fluid
- Therefore, IHL-216A may be a candidate for one or more of the FDA expedited review programs, to be submitted subject to a successful Phase 2b trial:
    - Breakthrough designation
    - Accelerated approval
    - Priority review
    - Fast-track
- FDA expedited review programs further hasten the drug review process, reducing the time to commercialisation

IHL-216A – Clinical Rationale

- CBD exhibits a broad spectrum of potential therapeutic properties, including neuroprotective effects in TBI (Shohami et al., 2011; Schurman and Lichtman, 2017)
- Through a multi-target mechanism, CBD shows potent anti-inflammatory and anti-oxidant properties, previously demonstrated in acute episodes of brain damage (Hayakawa et al., 2007; Castillo et al., 2010; Hayakawa et al., 2010)
- BM Nguyen (2014) discovered that patients who presented to a trauma centre who screened positive for cannabis had better survival outcomes than those who did not
- In 2012 a randomized double blinded placebo-controlled phase II study was published in patients who were comatose as a result of severe TBI. This trial of 97 patients showed treatment with KN 38-7271 cannabinoid improved 1-month survival in these patients (Firsching et.al., 2012)
- The Impression drug discovery team hypothesise that there is an optimal fixed dose of APIs within IHL-216A which, given soon after head trauma, will reduce:
    - Neuro-excitation
    - Neuro-inflammation
    - Cerebral Blood Flow
    - Cerebral Oxygen Consumption
- The intention is the achievement of neuroprotection, defined as reduced neuronal cell death and damage. Co-administration of CBD with a halogenated volatile anaesthetic agent is thought to create synergism whereby the concentrations of both agents can be reduced significantly whilst achieving efficacy

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The release of this announcement has been approved by the Board of Directors of IHL.

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