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INCANNEX

Novel Cannabinoid Drug Discovery
Innovator Cannabinoid Drug Therapeutics

By Dr Sud Agarwal

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Snapshot from Chief Medical Officer

Dr Sud Agarwal

- Under the guidance of our new medical advisory board, IHL has commenced the full drug discovery process for cannabinoid products for Sleep Apnoea, TBI and TMD. The expanded clinical program will create 3 novel products for which patents have been or are in the process of being filed.
- The program now facilitates a pathway to creating unique globally significant products for which registration will be sought from the TGA, FDA, EMA and other regulatory bodies.
- This program also can be achieved without sacrificing existing timelines for sale of products under the Special Access Scheme as previously announced to market, despite the expansion to the clinical programs for each product.
- Lastly, IHL is progressing its program on periodontitis with AXIM biotech and dental key opinion leaders to fast-track product knowledge and ultimately sales. A Drug discovery program for an IHL proprietary product oral care product is also being investigated.

Incannex – Medical Advisory Board

Dr Sud Agarwal

MB ChB, BSc (Hons), FANZCA

Specialist Anaesthetist

Chief Medical Officer - IHL

Non-Executive Director - IHL

Swinburne Medicinal Cannabis Research Collaboration - Research Fellow

Australian Expert on Novel Cannabinoid Research

Dr. Simon Hinckfuss

BDSc DCD (Melb) Cert Perio MS (Minn, USA)

Specialist Endodontist

Specialist Prosthodontist

Clinical Lead on Gingivitis

Assoc. Professor Michael Stubbs

BDS MDS MDSc FRACDS MRACDS

Clinical lead advisor on TMJ Trial

Assoc Professor – Latrobe University

Lecturer - University of Melbourne

Dr Ron Jithoo

MBChB, FRACS, FCS (SA), FICS

Clinical lead advisor on Traumatic Brain Injury Trial

Neurosurgeon (Alfred Hospital)

Neurosciences Reseacher - Research Fellow

National Trauma Research Institute

Dr David Cunnington

MBBS MMedSci DBSM RPSGT FRACP FAASM FCCP

Clinical lead advisor on Obstructive Sleep Apnoea Trial

Sleep Physician, St Vincents Hospital, Melbourne

Additional Research Staff from the Medicinal Cannabis Research Collaboration Engaged in the Incannex Preclinical and Clinical Research

Prof. Con Stough

BSc PhD

Medicinal Cannabis Research Collaboration (MCRC) Research Lead

Global Expert in Illicit Drug Research > 500 publications/ presentations

Head of Swinburne Human Psychopharmcology Department

Dr. Sarah Catchlove

BSc (Hons), PhD.

Medicinal Cannabis Research Collaboration (MCRC) Clinical Trials Coordinator

Dr. Gal Wong

MBBS (Melb. Uni)

Medicinal Cannabis Prescriber and Cannabinoid Drug Discovery Researcher

Drug Discovery Stages

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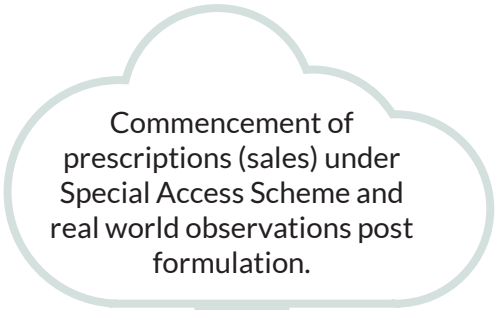

Drug	Therapeutic Area
IHL-42X	OSA
IHL-493C	TMJ
IHL-216A	TBI
IHL-668A	Gingivitis

Preclinical Research — Clinical Trial

Clinical Validation Gateway Study → Patent Filed for Novel Cannabinoid Drug → Formulation of Drug → In-vitro Studies → In-vivo Studies → Phase 1 → Phase 2 → Phase 3 → Phase 4 (Post-Marketing Surveillance)

Note: The Periodontitis trial will go ahead as the previously announced Phase 2A investigation trial of 30-40 participants following API dosage increases as advised by medical advisory board".

Modus Operandi for Therapeutic Areas Selected for Drug Discovery

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- To create first-in-class, innovator cannabinoid drugs where the therapeutic class shares several common properties:
- Total addressable market of each therapeutic area > $1Billion
- No existing pharmacotherapy options currently available and so the probability that the drugs being discovered will be eligible for public subsidies (e.g. PBS in Australia)
- Global export potential
- Accelerated commercialisation pathways remain available (e.g. early sales under Australian Special Access Scheme prescribed by willing doctors under the Cannvalate network prior to full product registration)
- Established body of research evidence validating hypothesis for cannabinoid working in the chosen therapeutic area
- A variety of near-term catalysts resulting from extensive multi-pronged clinical program, including open label studies, patent filings, in-vivo, in-vitro, human clinical trials etc.
- Investigating drug discovery program for oral health division currently underway to compliment existing periodontal clinical trial.

Three Fold Business Model

1. Development of targeted and scientifically validated products to market (long term value creation)
2. Potential early out-licensing of specialist products
3. Commercial commencement of certain cannabinoid therapies under Special Access Scheme (SAS) (immediate revenue)

Therefore allowing:

- Risk diversification
- Medium-longer term value creation
- Near-term revenue

Competitive Advantage

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Australia's Special Access Scheme gives it a unique position in the world for novel CBD drug development and testing

Within this advantaged framework, IHL has:

- A highly credentialed medical advisory board of global key opinion leaders in their respective fields
- A clear go-to-market strategy for development of novel pharmaceuticals
- 1 patent filed and a further 2 imminent
- 4 approved clinical programs

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IHL-216A

Traumatic Brain Injury Cannabinoid

Novel Cannabinoid for Traumatic Brain Injury (IHL-216A)

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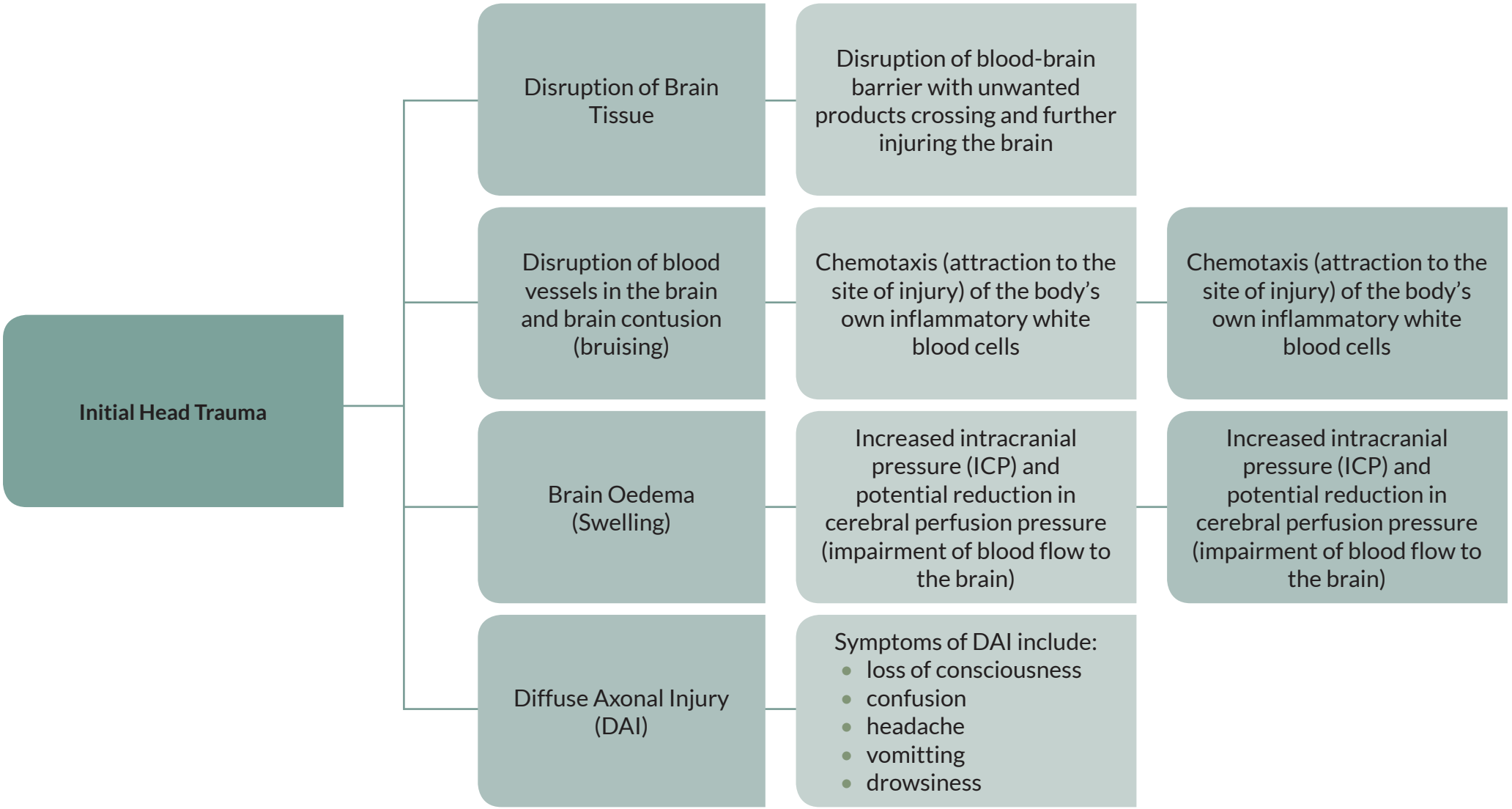
- Novel cannabinoid therapy led from the Swinburne Medicinal Cannabis Research Collaboration (MCRC) for the treatment of traumatic brain injury (TBI)
- Traumatic brain injury accounts for approximately 10 million deaths and/or hospitalization annually in the world (*Schuman et al., 2017*)
- There are currently no pharmaceutical agents approved for the treatment of TBI. IHL-216A is a world first concept
- Current treatment of major TBI is primarily managed through surgical intervention by decompressive craniotomy (*Bullock et al., 2006*) which involves the removal of skull segments to reduce intracranial pressure.
- The craniotomy procedure is associated with considerable complications, such as hematoma, subdural hygroma, and hydrocephalus (*Stiver, 2009*).
- Experimental drug IHL-216A is currently in pre-clinical testing

How a head injury causes damage to the Central Nervous System (CNS)

- The initial insult produces an immediate mechanical disruption of brain tissue (*Reilly, 2001*). This primary injury consists of contusion, blood vessel disruption and brain oedema, localized necrotic cell death, as well as diffuse axonal injury producing degeneration of cerebral white matter (*Adams et al., 1989; Gaetz, 2004*).
- Secondary injury mechanisms are initiated within minutes, in which necrotic and apoptotic cell death in contused areas and pericontusional penumbra continue over a period of days to months (*Raghupathi, 2004*).
- Injury-induced activation of CNS resident glial cells, microglia, as well as recruitment of circulating inflammatory cells, e.g., macrophages, then produce:
    - Secretion of inflammatory mediators, cytokines and chemokines (reviewed in *Woodcock and Morganti-Kossmann, 2013*).
    - Increased intracranial pressure leads to reductions in cerebral blood flow (*Shiina et al., 1998*)
    - Injury-induced breakdown of the cerebrovascular endothelium contributes to dysfunction of the blood-brain barrier (*Chodobski et al., 2012*).

Sequence of Events After TBI



How the Brain Responds Normally to TBI

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- In response to TBI, the brain normally increases the production of endocannabinoids (naturally occurring cannabinoids in the brain) by a factor of up to 10-fold (*Pankashvilli et al., 2001*).

These endocannabinoids are neuroprotective via several mechanisms:

- Reduction in brain electrical activity/excitation causing tissue damage
- Reduced neuroinflammation and reduced attraction of inflammatory cells
- Reduced brain vascular disruption and damage

Evidence supporting the use of Cannabinoids for prevention of TBI

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The journal of Neuroscience (2002) reported that the impact of induced cerebral ischemia is much more severe in mice who were genetically born with no cannabinoid receptors than normal mice with cannabinoid receptors

In 2012 a randomized double blind. placebo controlled phase II study was publisehd in patients who were comatose as a result of severe TBI. This trial (97 patients enrolled) showed treatment with KN 38-7271 (a cannabinoid) improved 1-month survival in these patients (*Firsching et.al., 2012*)

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

Israel Detense Force (IDF) practitioners administer CBD or low-dose THC as a first-line treatment to IDF soldiers – and even enemy combatants – who suffer brain trauma

2017 – ASADA removes the ban on cannabidiol

2018 – WADA removes the ban on cannabidiol

2019 – UFC commences trial using CBD for mixed martial arts fighters after fights to reduce post-trauma brain inflammation and swelling

Proposed mechanism of action of IHL-216A

- IHL-216A is a novel cannabinoid drug formulated to rapidly cross the blood brain barrier and act as an exogenous cannabinoid mimicking the actions of endocannabinoids on the central nervous system

The drug will be validated for its ability to:

- Reduce neuroinflammation
- Minimise disruption of brain vascularity
- Prevent increased intra-cerebral pressure and brain oedema after TBI

Estimated Market Size

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- **10 Million** patients globally affected by moderate-severe traumatic brain injury
- **>$1Billion** potential market value
- Prophylactically (preventative) administered drug needed in the immediate time period after head injury to prevent brain injury from developing
- No existing TGA/ FDA registered pharmacotherapy exists and so potential for orphan designation, fast-track licensing exist.
- Aiming to be a first-line therapy for traumatic brain injury globally

Summary of IHL-216A

- TBI is a massive cause of morbidity with a **total addressable market > $1Bn**
- Cannabinoids already thought to be effective in disrupting the mechanism of cellular brain damage after TBI with empirical evidence from animal, preclinical and retrospective human studies
- Cannabidiol (vaped) now widely and openly used by MMA fighters and boxers to prevent brain injury after repeated head injury during combat sports
- IHL-216A formulated to cross the blood-brain-barrier immediately after head injury and reduce the magnitude of neuro-inflammation which is one fo the main mechanisms of brain cellular injury after head trauma

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IHL-42X

Obstructive Sleep Apnoea

Obstructive Sleep Apnoea

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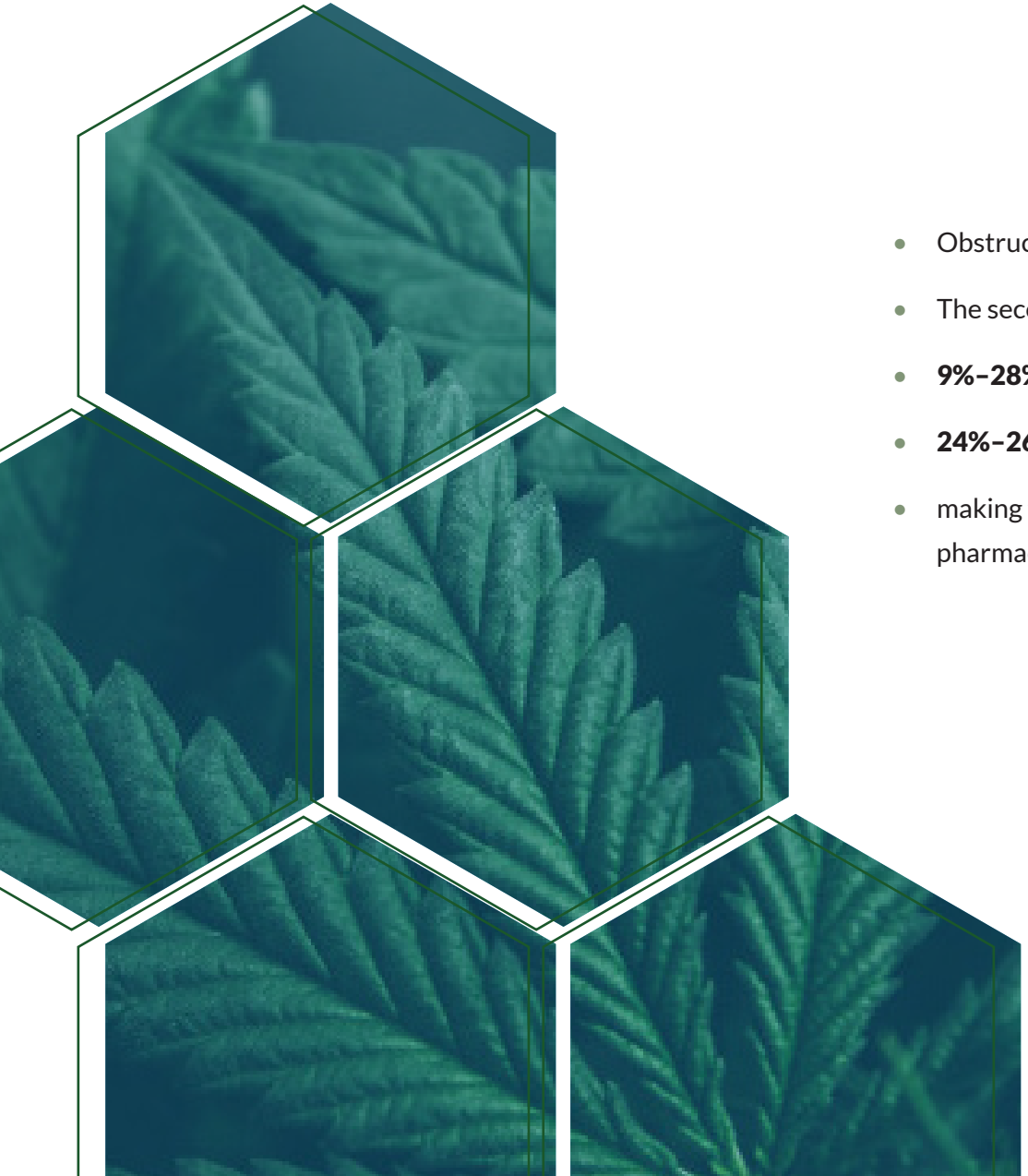

- Obstructive sleep apnea (OSA) is a common problem.
- The second most diagnosed respiratory condition after asthma
- **9%–28% of women** have apnoeic events at a treatable level
- **24%–26% of men** have apnoeic events at a treatable level
- making this the largest cause of chronic pathology for which no pharmacological treatment exists today

Economic Impact on Australia

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Deloitte.
Access Economics

- Deloitte Access Economics (2011) estimated the direct economic costs due to OSA were $21.2 Billion. This is through the loss of work days and morbidity caused by OSA through:
  - Coronary artery disease
  - Stroke
  - Congestive heart failure
  - Depression
  - Motor vehicle accidents (MVAs)
  - Workplace accidents
  - Type 2 diabetes

Existing Treatments

- The only public funded treatment for OSA currently in Australia, UK and USA is Continuous Positive Airways Pressure (CPAP) which is a mask worn at night linked to a machine used to generate high air pressures to splint the airways open
- CPAP is effective in reducing the severity of OSA and also reducing the incidence of the secondary complications of OSA such as MVAs, workplace accidents, coronary artery disease, stroke, diabetes etc
- However, long term compliance with CPAP has been shown to be poor with some papers suggesting almost 50% of people have abandoned treatment after only a short time due to:
  - Noise and discomfort of apparatus
  - Dislike of CPAP/difficult to use during travel
  - Claustrophobia with mask
  - Lack of affordability
  - Complaints from spouses/partners

Current Evidence on Cannabinoids in OSA

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- Carley et al (SLEEP Journal, 2018) showed that dronabinol reduced the severity of OSA by > 30%. This result has been replicated in3 other studies showing that cannabinoid therapy is an effective pharmacological treatment in OSA.
- However, there were some adverse events which limited the potential of the treatment
- IHL-42X is a novel cannabinoid pharmacotherapy which has been designed to share the effectiveness of Carley's experimental findings but with patent pending modifications designed to limit the adverse effects which limited its widespread use and tolerability.

How Cannabinoids work for OSA

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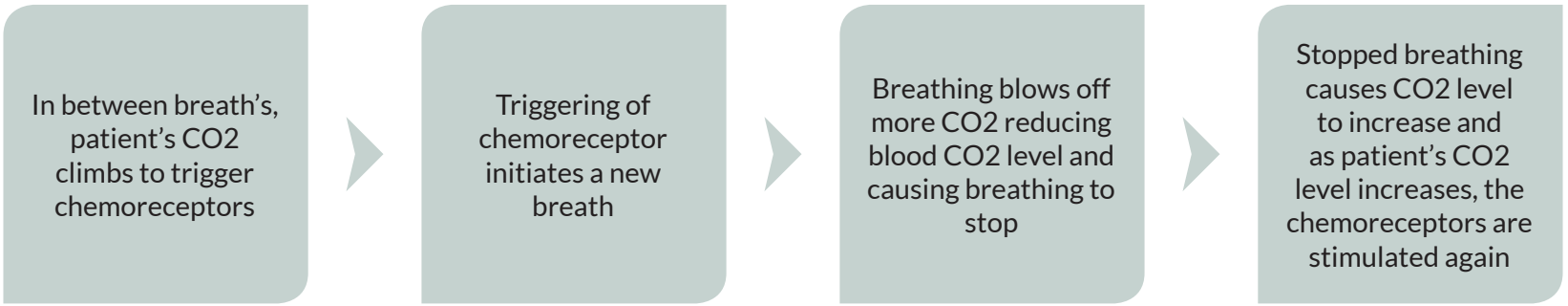
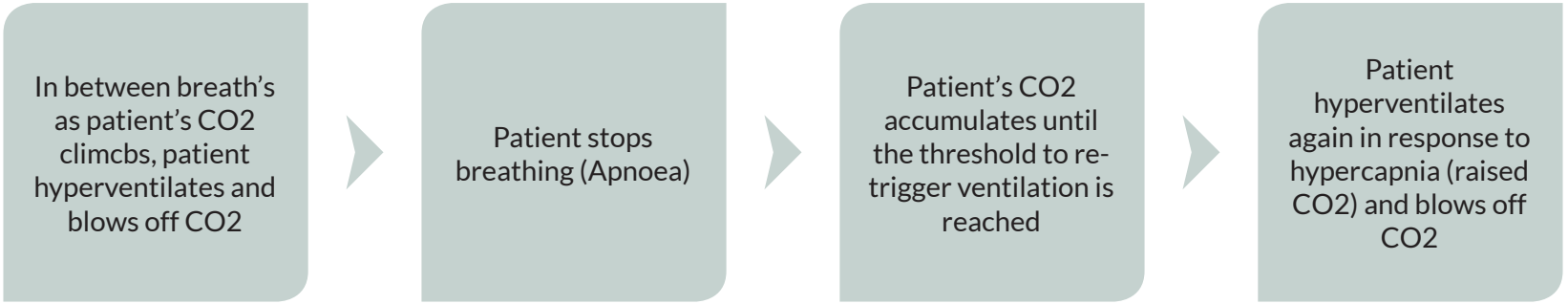
Normal People with normal chemoreceptor sensitivity



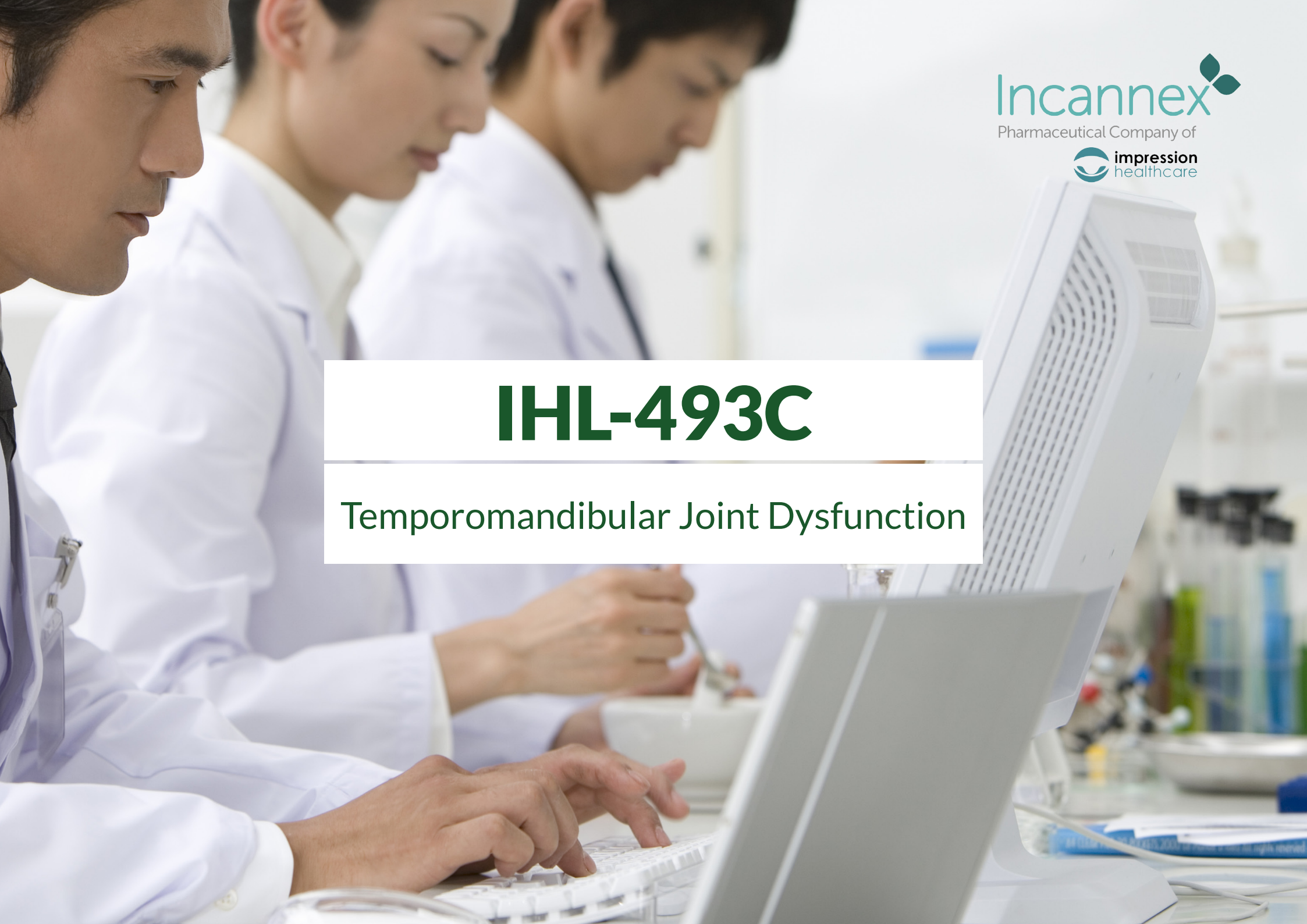
Normal People with extra-sensitive chemoreceptors (enhanced peripheral chemoreceptor sensitivity or excessive "Loop Gain" of chemoreceptor response)



Dronabinol (THC) helps reset the chemoreceptors to return to the baseline level of "Loop Gain" or more physiological level of chemoreceptor sensitivity. However, high levels of Dronabinol were associated with high levels of Adverse Reactions which could limit their medical use. IHL-42X is a novel cannabinoid therapy allowing the THC dose to be minimised whilst still remaining efficacious through additional constituents acting synergistically.

Summary of IHL-42X

- OSA is a massive unmet need with **total addressable market > $1Bn**
- Dronabinol already shown to be effective in treating OSA
- Improvements to enhance clinical performance underway by Incannex team
- IHL-42X is a novel cannabinoid designed to allow lower Dronabinol active dose to achieve same efficacy with reduced adverse effects
- Sales under SAS achievable post formulation



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IHL-493C

Temporomandibular Joint Dysfunction

Temporomandibular Joint

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- The temporomandibular joint (TMJ) is the joint that connects the jaw to the temporal bones of the skull.
- Temporomandibular joint disorder, known more commonly as TMD, occurs when there are problems with the muscles and jaws in the face
- There are many signs and symptoms of TMD including:
    - Pain in the face, jaw or ear area
    - Headaches (often mimicking migraines)
    - Earaches, and pain and pressure behind the eyes
    - A clicking or popping sound when opening or closing the mouth
    - Jaw that “gets stuck,” locked “lock jaw” or goes out of place
    - Tenderness of the jaw muscles
    - Swelling of the face

TMJ Dysfunction

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- TMD is a common condition, signs of which appear in up to 60–70% of the population
- The peak incidence is seen in adults aged 20–40 years
- Women are at least four times as likely to suffer from the disorder
- Despite signs of TMD being common, the reported prevalence of symptomatic disease requiring treatment occurs in only 5% to 12% of the population
- The National Institutes of Health (NIH) and the National Institute of Dental and Craniofacial Research (NIDCR) estimate that $4 billion is spent every year on the diagnosis and treatment of temporomandibular joint dysfunction in the USA alone
- The global market size is estimated to be at least twice that of the USA market.

TMD Current Treatment Options

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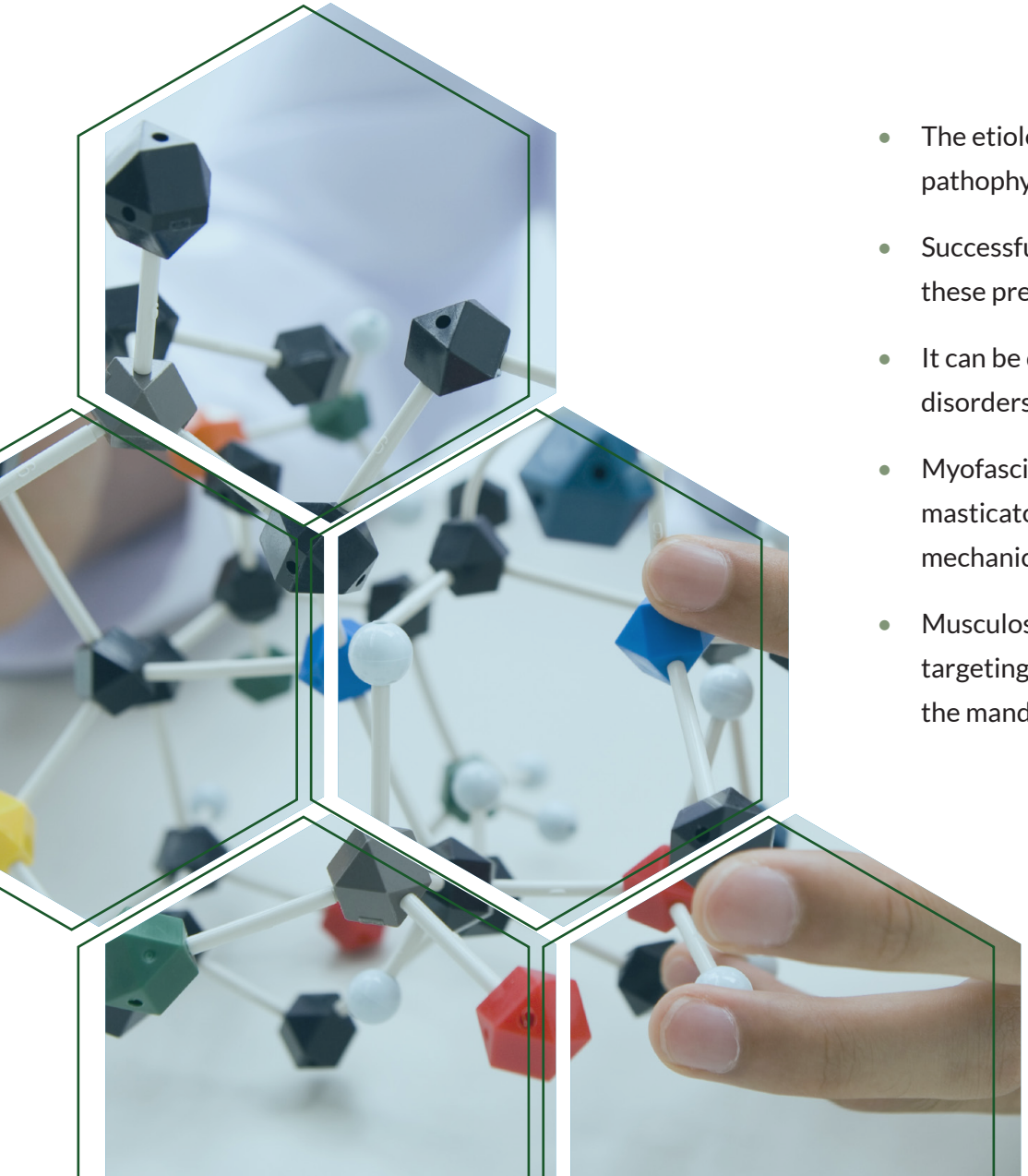
- There is no definitive pharmacological treatment available
- Mouth-guards, splints, anti-depressants and anxiolytics are widely used to
- reduce symptoms with varying levels of success
- A/Professor Michael Stubbs is recognised Australian expert in TMD and treats several thousand patients a year with TMD and atypical facial pain
- The Incannex patent pending IHL-493C contains a novel cannabinoid API and novel excipients to directly target the site of pain and symptoms

Pathology of TMD



- The etiology of TMD is likely to be multifactorial and includes anatomical, pathophysiological and psychosocial factors.
- Successful management of the disorder involves identifying and managing these predisposing and contributing factors
- It can be divided up between myofascial causes of TMD and intra-articular disorders of the joint itself
- Myofascial disorders are the result of tension, fatigue or spasm of the masticatory (chewing) muscles, whereas intra-articular disorder stems from mechanical or inflammatory disruption of the joint itself.
- Musculoskeletal dysfunction is the most common cause of TMD and drugs targeting muscle stiffness, ligament tightness, muscle and joint pain around the mandible and facial area

Why Cannabinoids?

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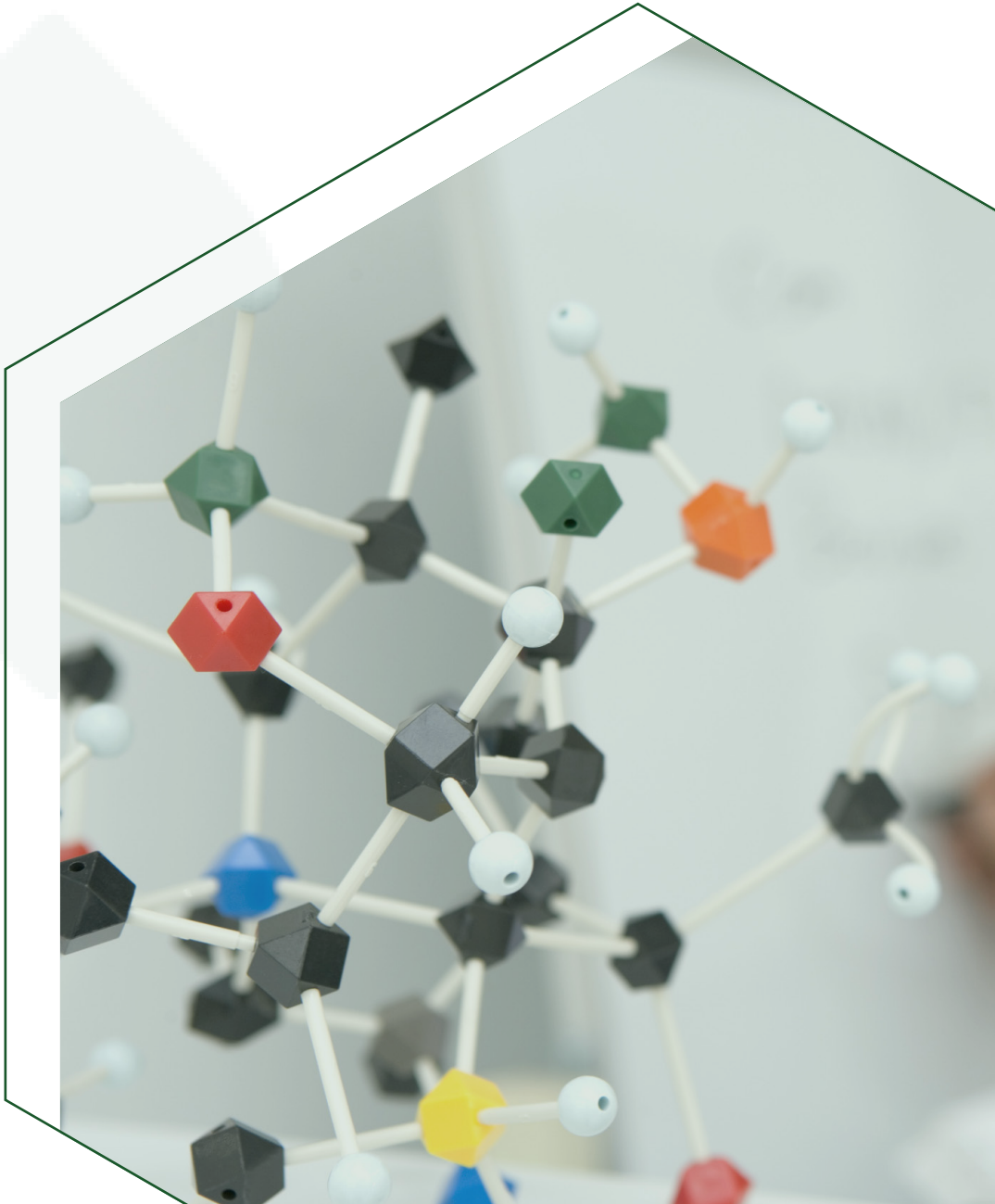
- Cannabinoids are increasingly commonly used for muscle and tendon stiffness and spasticity in diseases such as multiple sclerosis and cerebral palsy.
- There is substantial evidence suggesting that cannabinoids have local analgesic and anti-inflammatory effects if given in high enough concentrations



Mechanism of action of IHL-493C

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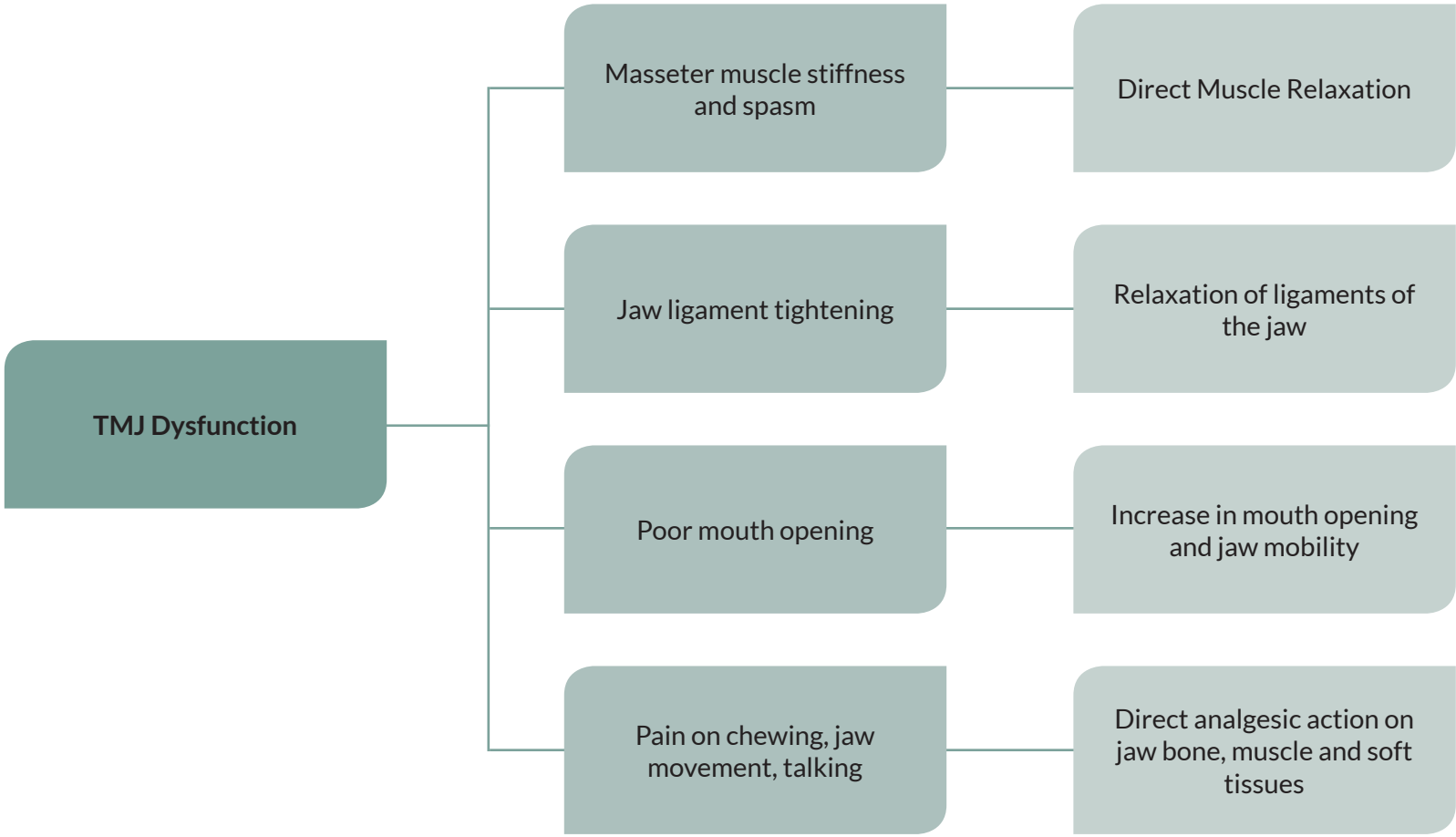

Summary of IHL-493C

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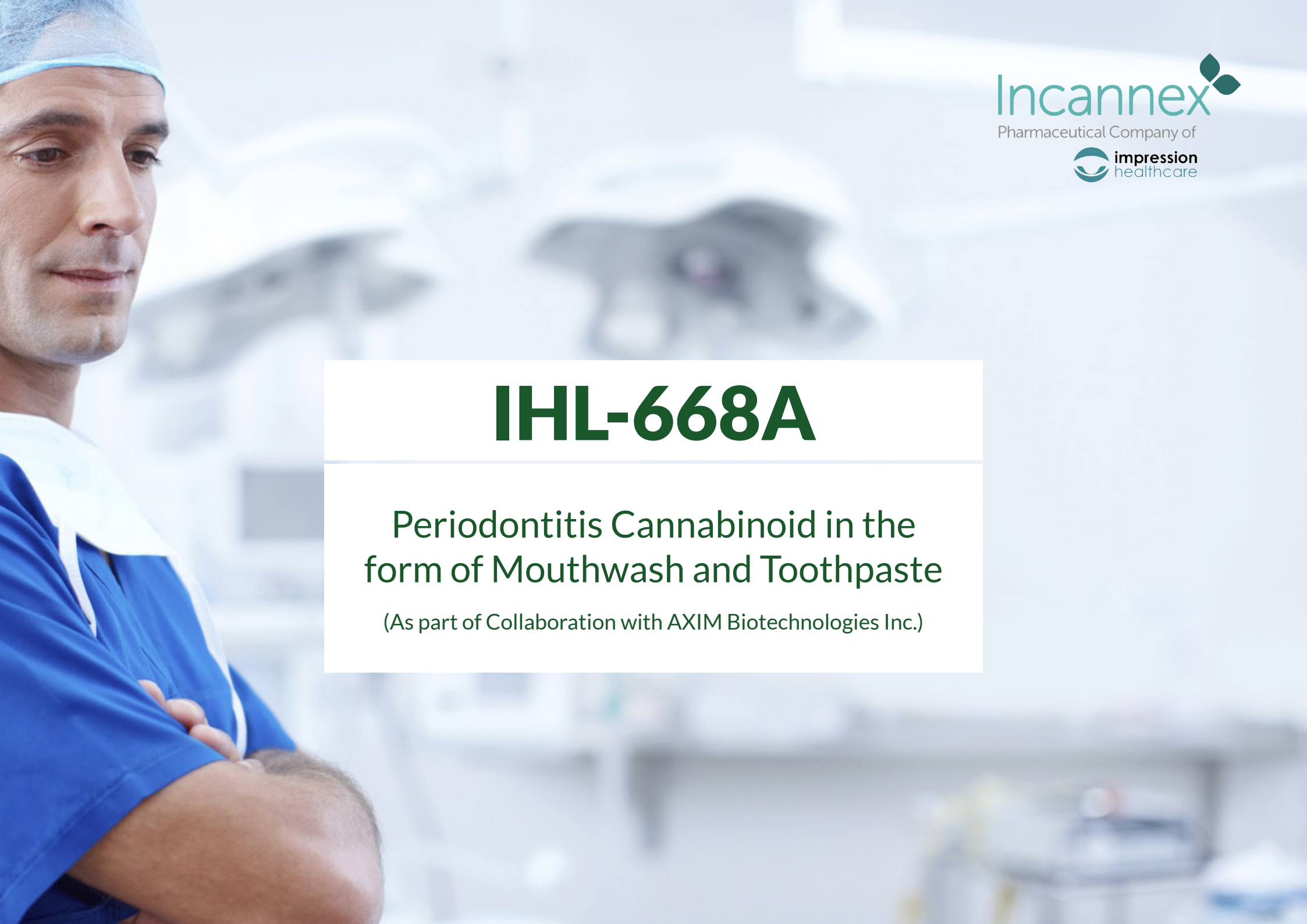
- TMD affects 20% of the adult population
- There is no current approved pharmacotherapy and the first line therapy used is mostly conservative and symptomatic management
- The amount of money spent on treatment for **TMD >$8Bn**
- Cannabinoids have been show in animal models to reduce pain and inflammation transdermally
- IHL-493c is a novel, patent-pending investigational drug designed and formulated for the sole purpose of treating TMD transdermally



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IHL-668A

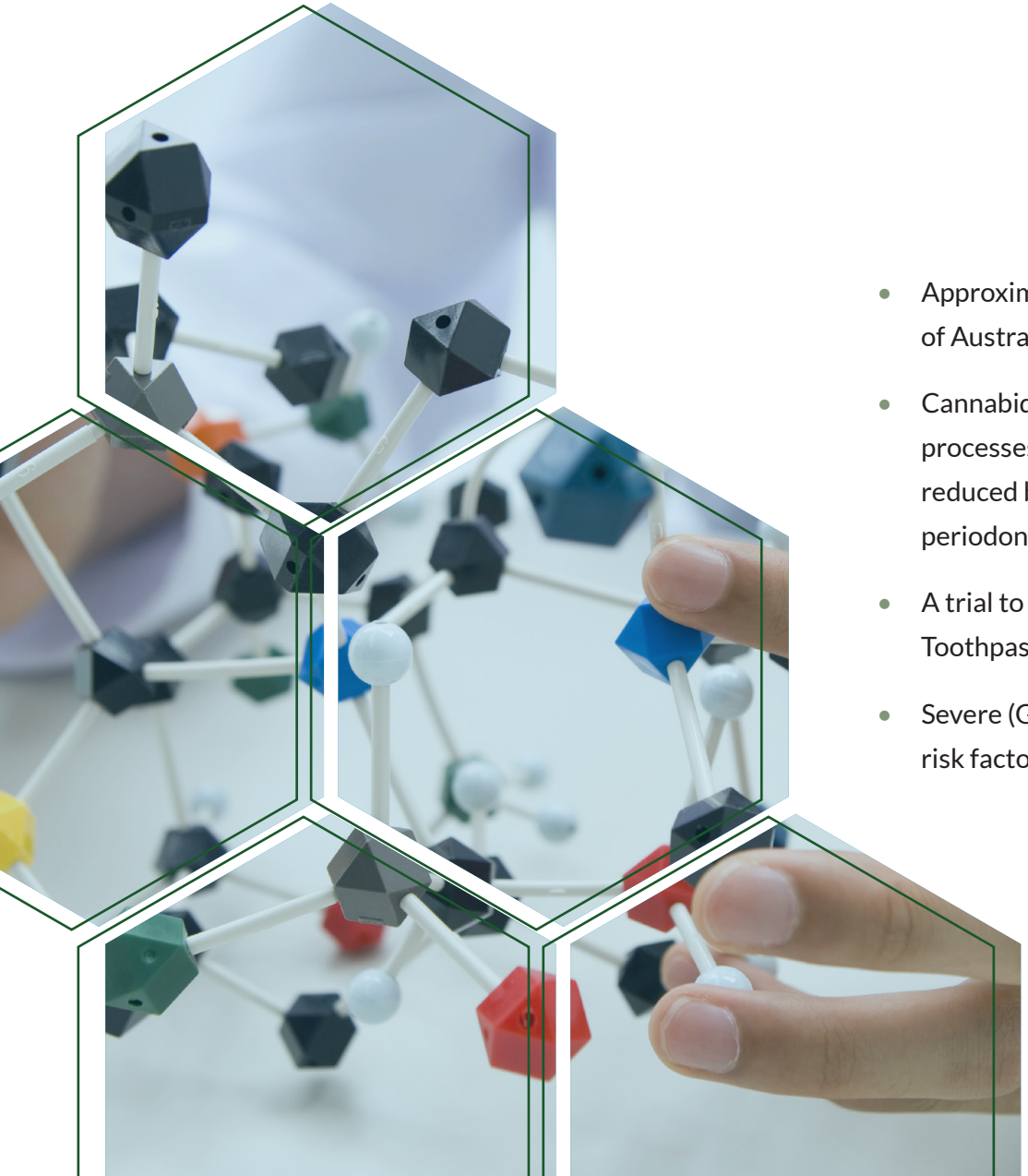
Periodontitis Cannabinoid in the form of Mouthwash and Toothpaste

(As part of Collaboration with AXIM Biotechnologies Inc.)

Mouthwash and Toothpaste for Periodontitis

- IHL has first right of refusal over all current and future AXIM products for 3 years, until May 2022
- Exclusive license granted to Impression over CBD-based mouthwash and toothpaste targeting Gingivitis and Gum Disease, known formally as Periodontitis or Periodontal Disease, for sales in Australia and New Zealand
- Trial protocol has been finalised, the pending trial registered with the ANZCTR, to be overseen by Dr Simon Hinckfuss
- Refinement and “dosage up” of product formulation currently underway prior to patient administration

Size of Australian Market and Medical Action



- Approximately 20% of the Australian population (5M people), and almost 40% of Australians aged 55 years or over, have moderate-to-severe periodontitis
- Cannabidiol (CBD) is known to be a potent suppressor of inflammatory processes by inhibiting the expression of cytokines and this can cause reduced bone resorption and can reduce the rate of bone loss coincident with periodontitis
- A trial to examine the benefits of Cannabidiol (CBD) Mouthwash and Toothpaste to reduce the grading of Periodontitis compared to a placebo
- Severe (Grade 4) Periodontitis can lead to tooth loss, bone damage and is a risk factor for heart and lung disease

Incannex Summary

- IHL have 3 novel innovator drugs with global patents filed or under submission
- Fourth proprietary product and program being investigated to compliment mouthwash and toothpaste program being undertaken with AXIM.
- All 3 are backed and designed by Specialist Key Opinion Leaders at the highest level of clinical and research expertise in Australia
- In-vitro, in-animal or in-human data exists in the medical literature suggesting the utility of cannabinoids in each of the therapeutic areas.
- First batch of CBD oils expected to be received for SAS prescription in the week commencing 14th of October 2019

Market Value Comparison

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	Novel Cannabinoids	Existing Competitors for drugs under discovery	Market Capitalisation ($ Million)
Botanix	3	10+	$226
GW Pharma	2	10+	$3,200
Zynerba	4	0	$163
Medlab	2	10+	$95
Impression Health	3	0	$48