Date: 15th April 2020
ASX Announcement (ASX: IHL)

Impression investigating IHL-675A for potential treatment of sepsis associated ARDS, leading cause of mortality from COVID-19 and other infections

Highlights:

- Impression is developing IHL-675A, comprising hydroxychloroquine and cannabidiol ('CBD'), for the potential treatment of sepsis-associated Adult Respiratory Distress Syndrome ('ARDS')
- Sepsis associated ARDS is caused by a hyper-inflammatory response
- CBD displays potent anti-inflammatory activity
- Hydroxychloroquine has been used off-label for the treatment of inflammatory lung diseases
- Sepsis associated ARDS is the leading cause of mortality associated with severe infections, including the COVID-19 coronavirus infection[1, 8]
- IHL to commence animal testing for IHL-675A after the receipt of an import permit for CBD into Taiwan testing facility
- On the 9th of April 2020, Impression lodged a provisional patent application over IHL-675A for ARDS with the Australian Patent Office.

Impression Healthcare Limited ('Impression', 'IHL' or the 'Company'), announces that it is developing a novel small molecule therapeutic IHL-675A comprising hydroxychloroquine and cannabidiol ('CBD') for the potential treatment of sepsis-associated Adult Respiratory Distress Syndrome ('ARDS'), a major unmet clinical need and the leading cause of mortality associated with COVID-19 infection[1].

Impression has lodged a provisional patent application over IHL-675A for ARDS with the Australian Patent Office as it continues development activities. The inventors are Impression's own Chief Medical Officer, Dr Sud Agarwal and Chief Scientific Officer, Dr Mark Bleackley. The Company has engaged a specialist pharmaceutical research organisation Eurofins Scientific Taiwan ('Eurofins') to conduct animal pre-clinical testing of the IHL-675A combination once the relevant permit is received. Eurofins' Taiwan location has been selected as IHL's research provider because Taiwan has ample stores of hydroxychloroquine required for the studies. The studies are expected to commence soon after the receipt of CBD by Eurofins from IHL, which will be after the receipt of a CBD import permit from the Taiwanese authorities.

The pathogenesis of sepsis associated ARDS is as follows:

1. **Viral or bacterial infection** leads to the body releasing chemicals such as histamine and prostaglandins into the blood stream to induce inflammation and recruit white blood cells to fight the infection. When this process is over activated, dysregulated, or otherwise out of balance, sepsis occurs[2,3,4]

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2. Cytokines, a family of molecules that are secreted by white blood cells to mediate an inflammatory response, recruit more white blood cells to the site of infection to eliminate the virus or bacteria. In some patients, cytokine production during sepsis is excessive culminating in a **'cytokine storm'.** A cytokine storm is a hyperinflammatory response, a rapid overreaction of the immune system, where overproduction of white blood cells is activated and they in turn release more inflammatory cytokines, which in turn activate yet more white blood cells. This process can go on to damage the host tissues and organs[5].
3. When the lungs are damaged by the hyperinflammatory response **sepsis associated ARDS** is said to be occurring (characterized by widespread inflammation of the lungs)[6].

Sepsis associated ARDS is characterized by hyperinflammation, capillary leakage, and pulmonary oedema ('wet lung') resulting in breathing difficulties (dyspnea), rapid breathing (tachypnea), excessively deep and rapid breathing (hyperventilation), and insufficient levels of oxygen in the circulating blood (hypoxaemia). Respiratory failure may ultimately lead to multiorgan failure and death[7].

Sepsis associated ARDS is the leading cause of mortality associated with COVID-19 coronavirus infection[8]. IHL-675A is potentially a new treatment for COVID-19 ARDS, and all other serious infections leading to sepsis associated ARDS.

Rationale for IHL-675A

The clinical objective of ARDS treatment is the reduction of the acute pulmonary inflammatory response, reversal of pulmonary oedema, and limitation of damage to the lung. Resolution of the immune response not only includes dampening of inflammation, but also promotion of immune system regulatory pathways, which may reverse tissue damage.

The potential for IHL-675A is that the two compounds within it (CBD and Hydroxychloroquine) appear to work in different manners to quell the inflammation response to infections.

Cannabinoids are potent anti-inflammatory agents and they exert their effects through multiple pathways[9]. CBD acts through suppression of subsets of immune cells, activation of regulatory cells and induction of cell death[10]. A study on cytokine production in an asthma animal model demonstrated that CBD greatly reduces cytokine production during lung inflammation[11].

Hydroxychloroquine is an immunomodulatory molecule that reduces activation of T-cells and interferes with pro-inflammatory signaling[12]. Hydroxychloroquine also exhibits an antiviral effect and has recently been associated with the attenuation of patients to severe progression of COVID-19[6].

The immunomodulatory activity of hydroxychloroquine has led to it being used to treat the auto-immune disease Lupus. There is also evidence to support a benefit for hydroxychloroquine in treatment of lung diseases. Treatment with hydroxychloroquine reduced the inflammatory response in an animal model of lung injury[13]. It has also been previously prescribed by doctors "off-label" for the treatment of inflammatory lung diseases[14].

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Hydroxychloroquine has also received substantial attention as a potential treatment for COVID-19 due to its anti-inflammatory activity as well as direct inhibition of the viral infection and release cycle. Treatment with hydroxychloroquine decreased the viral load in *in vitro* experiments[15].

A randomised controlled trial assessing the efficacy of hydroxychloroquine in 62 patients with COVID-19 was completed at the Renmin Hospital of Wuhan University in February. The conclusions from that trial were that body temperature recovery time and the cough remission time were significantly shortened in the hydroxychloroquine control group. Additionally, 4 patients who progressed to severe illness were from the placebo group[16].

The potential ability to translate the potent anti-inflammatory and immunomodulatory properties of IHL-675A to a clinical setting for the treatment of sepsis-associated ARDS is further encouraged by the "druggability" properties of IHL-675A, including:

- high oral bioavailability of Hydroxychloroquine,
- chemical stability of both Hydroxychloroquine and CBD, which assures long-term shelf-storage, and
- high potency of both active pharmaceutical ingredients.

IHL-675A Development Plan

Once the relevant permits are obtained, the IHL-675A Development Plan, to be funded from existing IHL cash reserves, will proceed as follows.

Firstly, the ability of IHL-675A to reduce cytokine production and hyperinflammation will be defined in a classic rodent model of sepsis. This will establish the optimal ratio of the two drugs, establish the potent anti-inflammatory activity of the combination and ability to minimize the cytokine storm, the key mediator of ARDS.

If a successful proof of concept of IHL-675A in animal studies can be established, FDA consultants Camargo Pharmaceutical Services has advised IHL and IHL-675A will be a strong candidate for FDA Emergency Use Authorisation resulting from the COVID-19 Pandemic. The designation of Emergency Use Authorisation would facilitate an expedited investigational new drug (IND) meeting with the FDA, which would facilitate the commencement of clinical trials in which IHL would test IHL-675A in patients with COVID-19. Hydroxychloroquine as a standalone therapeutic was given Emergency Use Authorisation in a letter from the FDA dated the 28th of March 2020[17].

Subject to animal pre-clinical success, IHL has also designed a pharmaceutical development program for IHL-675A in order to pursue registration in the seven major markets by the cognizant regulatory bodies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Of course, it is by no means certain that the relevant permit will be received by Eurofins to import CBD to Taiwan or that the in animal studies will be successful. Even if the animal studies are successful, it is not certain that IHL-675A will be designated FDA Emergency Use Authorisation. A failure or delay at any stage of the Development Plan would adversely affect IHL's ability to conduct clinical trials for IHL-675A and obtain registration for IHL-675A in the relevant markets.

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Current Treatment Options for sepsis associated ARDS are Limited

There are currently no registered pharmaceutical agents for the treatment of sepsis associated ARDS. It is treated with mechanical ventilation and oxygen supplementation in an intensive care unit. Mechanical ventilation is usually delivered through a rigid tube which enters the oral cavity and is secured in the airway (endotracheal intubation), or by tracheostomy when prolonged ventilation (≥2 weeks) is necessary[18]. Treatment of the underlying cause is crucial. Appropriate antibiotic or anti-viral therapy must be administered as soon as infection is suspected.

Completion of CBD Mouthwash and Toothpaste Clinical Program with AXIM

IHL has ceased all licensing activities with AXIM Biotechnologies Inc. ('AXIM'). IHL had previously indicated that it would purchase CBD-based toothpaste and mouthwash from AXIM for a clinical trial into their use for the treatment of periodontitis (gum disease and gingivitis).

IHL has ceased the periodontitis program to focus on the creation of products that have no existing pharmacotherapy options, global export potential and addressable markets exceeding $1B per annum, which now includes IHL-675A for sepsis associated ARDS. Sales of AXIM mouthwash and toothpaste would have been limited under license to the Australian market through the Special Access Scheme. As part of the completion of the arrangement, AXIM has ceased to hold any shares previously issued to it in connection with the relationship.

The release of this announcement has been approved for issue by IHL's Board of Directors.

For further details on the announcement, interested parties should contact:

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ENDS

About Impression Healthcare Limited (ASX: IHL)

Impression Healthcare Limited (IHL.ASX) is developing unique medicinal cannabis products for the treatment of Obstructive Sleep Apnoea (OSA), Traumatic Brain Injury (TBI)/Concussion, Acute Respiratory Distress Syndrome (ARDS) and Temporomandibular Joint Disorder (TMD). FDA registration, where being sought, is subject to clinical success.

Each indication represents major global markets and currently have no existing registered pharmacotherapy (drug) treatment, raising the possibility of patients receiving Government subsidies for products that demonstrate suitable safety and efficacy profiles in clinical trials.

There is an established body of research validating the hypothesis for the cannabinoids being used in Impression's chosen therapeutic areas and IHL has a strong patent filing strategy (as announced "IHL files cannabinoid patent over IHL-216A for TBI" 04th October, 2019 and "IHL Files Patent over IHL-42X for OSA" 06th of December, 2019) as it develops its products in conjunction with its medical advisory board.

Further to its clinical programs, Impression has its Australian license to import, export and distribute medicinal cannabis products and has launched a line of cannabinoid oil products under the brand, "Incannex". The cannabis-based oils are sold under Impression's product supply and distribution agreement with Cannvalate Pty Ltd, which is the largest network of cannabis medicine prescribers in Australia.

Yielding growing revenues to Impression is its customised oral devices manufacturing business. The oral devices division delivers high-quality products both direct to the consumer and via a growing B2B preferred practitioner network of dentists.

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