Date: 17th July 2020
ASX Announcement (ASX: IHL)

Positive Results from Pre-Clinical Animal Study for the Assessment of IHL-675A Against Sepsis Associated ARDS; a Leading Cause of COVID-19 Mortality[1]

Highlights:

- Incannex has received positive results from its pre-clinical animal study for the assessment of the key constituents of IHL-675A against sepsis associated acute respiratory distress syndrome
- Compared to baseline mice, Cannabidiol reduced 5 key inflammatory cytokine levels by 31-90%, relative to the vehicle
- Compared to baseline mice, Hydroxychloroquine reduced 5 key inflammatory cytokine levels by 39-88%, relative to the vehicle
- Compared to mice that received the vehicle, Cannabidiol reduced the production of cytokine levels by a maximum of 19-44%
- Compared to mice that received the vehicle, Hydroxychloroquine reduced the production of cytokine levels by a maximum of 18-35%
- Results exceed internal expectations of 15% maximum reductions relative to the vehicle and 80% of results were deemed statistically significant
- Incannex is now proceeding immediately to stage 2 of animal studies and has arranged for an *in vitro* study that will commence imminently
- The second animal study to test for the optimal fixed dose combination will immediately follow the *in vitro* study
- Subject to success in stage 2, it is the opinion of FDA consultants Camargo Pharmaceutical Services that IHL-675A will be a candidate for FDA Emergency Use Authorisation resulting from the COVID-19 pandemic
- There is significant unmet need in the treatment of SAARDS and there are no registered pharmacotherapy (drug) treatments available for the condition[2].

Incannex Healthcare Limited (ASX: IHL, 'Incannex' or the 'Company'), is delighted to announce that it has received positive results from its pre-clinical animal study, conducted by Eurofins Taiwan, for the assessment of the key constituents of IHL-675A against sepsis associated acute respiratory distress syndrome ('SAARDS'). These results are contained in the appendix on pages 5-7 of this announcement. IHL is a clinical stage cannabinoid development company, with four cannabinoid-based clinical programs underway.

Rodent cohorts were dosed with either Cannabidiol ('CBD') or Hydroxychloroquine ('HCQ') in escalation, introduced to an inflammatory agent to induce sepsis, and then had their blood sampled 2 hours later. Five of the most vital cytokines associated with inflammation were measured.

The study was designed in this manner to:

1. Demonstrate the ability of CBD and HCQ to inhibit inflammatory cytokine production associated with Sepsis and Sepsis Associated ARDS; and,
2. assess the dose responses of Cannabidiol ('CBD') and Hydroxychloroquine ('HCQ') to the production of cytokine inflammatory markers in rodents after inducing sepsis to benefit the design of the fixed dose combination product.

CBD significantly reduced production of serum cytokine levels after the inflammatory stimulus and with a bell-shaped dose response curve. The maximum level of inhibition ranged from 19-44%, relative to cytokine levels in the vehicle treated mice. The "vehicle" being the delivery fluid that carried the CBD or HCQ.

HCQ also significantly reduced the production of serum cytokine levels after the inflammatory stimulus but with a linear dose response curve. The maximum inhibition of cytokine levels ranged from 18-35%, relative to the vehicle treated mice. The results for both CBD and HCQ compare favourably to IHL's expectation of greater than 15% cytokine inhibition, relative to the vehicle treated mice.

Compared to untreated rodents with no induction of sepsis ('baseline'), CBD reduced cytokine levels up to 90%, relative to the vehicle. Compared to the baseline rodents, HCQ reduced cytokine levels up to 88%, relative to the vehicle. These notable results were achieved with a single dose after only 2 hours.

Chief Scientific Officer of Incannex Healthcare, Dr Mark Bleackley, said; "The results from the study, using a well-established animal model of sepsis, are revealing and positive for the development of IHL-675A. Our goal is to develop a product that reduces acute inflammation to slow the development and reduce the severity of sepsis so that sepsis associated ARDS does not develop. The study has provided critical data that is informing the design of the combination product that will be tested in the next round of investigations".

Incannex is now proceeding immediately to stage 2 of its pre-clinical program that will commence imminently with Eurofins USA and Eurofins Taiwan conducting the research.

Generally, drug development of combination therapeutics attempts to design products with a greater therapeutic effect in a certain fixed dose combination than its constituent parts. Therefore, Stage 2 involves the investigation of the optimal inflammation dampening response of the IHL-675A combination drug. IHL has arranged for an *in vitro* study that will commence imminently and take approximately 5 weeks before results are published and the second animal study to test optimal fixed dosed combinations will commence thereafter.

Subject to success in stage 2 animal testing; it is the opinion of FDA consultants Camargo Pharmaceutical Services ('Camargo') that IHL-675A will be a candidate for FDA Emergency Use Authorisation resulting from the COVID-19 Pandemic. The designation of Emergency Use Authorisation could facilitate an expedited investigational new drug (IND) meeting with the FDA, which could facilitate the commencement of in-human clinical trials in which IHL would test IHL-675A in patients with COVID-19.

CEO and Managing Director of Incannex Healthcare, Mr Joel Latham, said; "We're delighted that the first set of trial results we have received from across our four clinical programs are positive, facilitating our decision to immediately move forward to the next step with confidence.

These results confirm our strategy to pursue cannabinoid-based clinical assets relevant to major markets in indications with unmet need and no registered pharmacotherapeutic options".

IHL previously announced that it filed a provisional patent over IHL-675A for SAARDS on the on the 15th of April 2020. In that same announcement, IHL detailed that the clinical objective of SAARDS treatment is the reduction of the acute pulmonary inflammatory response, reversal of pulmonary oedema, and limitation of damage to the lung.

What is Sepsis Associated Acute Respiratory Distress Syndrome ('SAARDS')?

Sepsis occurs when the immune system overreacts to an infection, producing excessive levels of cytokines, which are signalling molecules that attract immune cells[3]. Elevated levels of those cells secrete more cytokines, and this "cytokine storm" recruits even more immune cells, fuelling a cascading cycle that eventually damages host tissues and organs[4].

When the lungs are damaged by the cytokine storm hyperinflammatory response, SAARDS is said to be occurring. SAARDS is characterized by widespread inflammation of the lungs, often referred to as 'wet lung' or pneumonia, inhibiting the patient's ability to oxygenate blood[3]. SAARDS is a leading cause of mortality associated with COVID-19 coronavirus infection and is also a leading cause of mortality from other lung, urinary tract, stomach, and skin infections[5,6].

There is significant unmet need in the treatment of SAARDS and has been for many decades. The best treatment continues to be the use of oxygen ventilators to treat symptoms of ARDS, but not the underlying cause. There is currently no registered pharmacotherapy (drug) treatment for SAARDS, however, the global medical community continues to investigate numerous drug treatments in its search for a new standard of care in response to COVID-19 coronavirus.

ENDS

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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References:

[1]https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930628-0
[2]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5526960/#:~:text=Effective%20pharmacotherapy%20for%20ARDS%20remains,outcomes%20of%20these%20patients11.
[3]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429642/
[4]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294426/
[5]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4823184/
[6]https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext

About Incannex Healthcare Limited (ASX: IHL)

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

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APPENDIX

A mouse sepsis model was used to investigate the anti-inflammatory dose response for CBD and HCQ. Mice were pre-treated with 6 doses of CBD or HCQ 1 hour prior to the induction of sepsis by injection of bacterial lipopolysaccharide (LPS). LPS is a potent inducer of the cytokine production that is characteristic of sepsis. Blood samples were collected by cardiac puncture 2 h after LPS injection and analysed for cytokine levels using a Luminex assay. Each dosing cohort consisted of ten mice. Cytokine levels were normalised to baseline (mice with no LPS injection and no drug or vehicle treatment) and compared to those detected in vehicle (CBD vehicle 1:1:18 ethanol:Tween 20:saline, HCQ vehicle saline) treated mice. IFN-γ data was not normalised to baseline as there was an issue with baseline data. CBD generally displayed a bell-shaped dose response curve, whereas HCQ generally displayed a linear dose response curve.

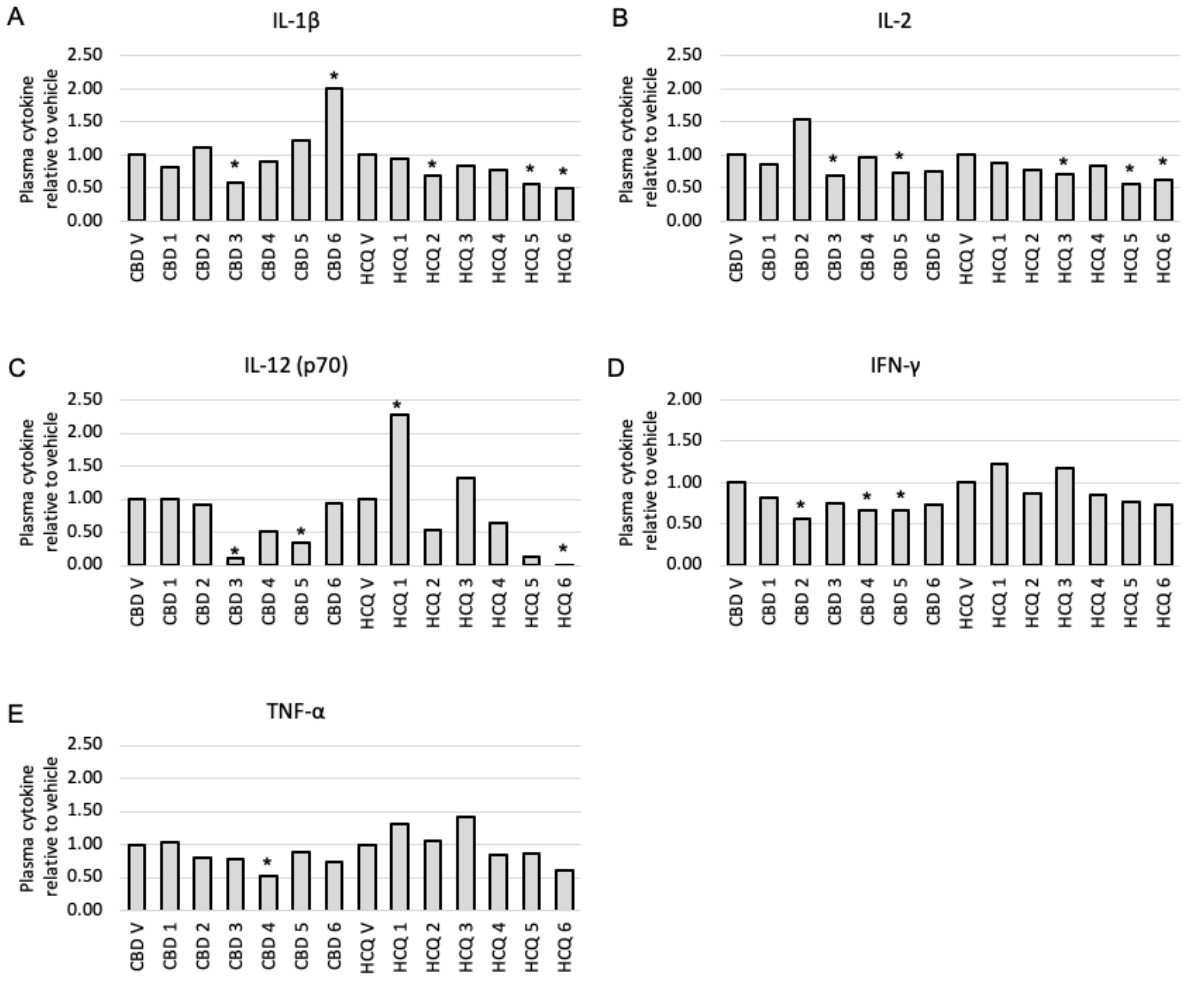

Figure 1. Reduction in cytokine levels on treatment with CBD or HCQ in a mouse sepsis model. Mice were pre-treated with CBD or HCQ 1 hour before induction of sepsis by injection of LPS. Blood samples were collected 2 hours after LPS injection and analysed for inflammatory cytokine levels (A) IL-1β, (B) IL-2, (C) IL-12 (p70), (D) IFN-γ, (E) TNF-α using a Luminex assay. Data for all cytokines except IFN-γ have been normalised to baseline. Values presented for all cytokine levels are relative to the vehicle control. Cohorts that differed significantly (p <0.1) from the vehicle treated cohort based on analysis of the non-normalised data are indicated by *.

Table 1. Cytokine levels in CBD and HCQ treated mice 2 h after LPS injection. The mean value for each cohort has been baseline normalised and is expressed relative to the mean for the respective vehicle with the exception of IFN-γ which has not been baseline normalised due to the cytokine levels being abnormally high in the baseline cohort.

	IL-1β	IL-2	IL-12 (p70)	IFN-γ*	TNF-α
CBD V	1.00	1.00	1.00	1.00	1.00
CBD 1	0.83	0.86	1.00	0.81	1.03
CBD 2	1.11	1.53	0.92	0.56	0.80
CBD 3	0.57	0.69	0.10	0.75	0.77
CBD 4	0.90	0.96	0.50	0.66	0.52
CBD 5	1.22	0.72	0.35	0.67	0.88
CBD 6	2.02	0.75	0.93	0.73	0.73
HCQ V	1.00	1.00	1.00	1.00	1.00
HCQ 1	0.95	0.88	2.27	1.24	1.31
HCQ 2	0.69	0.78	0.53	0.87	1.06
HCQ 3	0.83	0.70	1.33	1.17	1.41
HCQ 4	0.77	0.85	0.64	0.86	0.84
HCQ 5	0.56	0.56	0.12	0.76	0.86
HCQ 6	0.49	0.62	-0.03	0.73	0.61

not baseline normalised

Table 2. p-values for cytokine levels compared to vehicle treated mice. P-values were calculated based on comparison of the raw data (i.e. not normalised) for the cytokine at each doses of CBD or HCQ to the respective vehicle control using a two-tailed t-test with unequal variance in Microsoft Excel.

	IL-1β	IL-2	IL-12 (p70)	IFN-γ	TNF-α
CBD V	1.00	1.00	1.00	1.00	1.00
CBD 1	0.36	0.26	1.00	0.43	0.93
CBD 2	0.84	0.17	0.88	0.02	0.43
CBD 3	0.02	0.01	0.02	0.15	0.29
CBD 4	0.67	0.85	0.20	0.07	0.04
CBD 5	0.33	0.02	0.08	0.07	0.58

CBD 6	0.06	0.32	0.91	0.20	0.28
HCQ V	1.00	1.00	1.00	1.00	1.00
HCQ 1	0.80	0.46	0.07	0.33	0.29
HCQ 2	0.04	0.23	0.47	0.58	0.79
HCQ 3	0.23	0.06	0.62	0.47	0.24
HCQ 4	0.11	0.54	0.49	0.48	0.56
HCQ 5	0.01	0.01	0.13	0.25	0.58
HCQ 6	0.00	0.03	0.08	0.16	0.13