Date: 16th March 2021
ASX Announcement (ASX: IHL)

Incannex initiates sixth research program following more positive *in vivo* results; IHL-675A for rheumatoid arthritis

IHL-675A has been demonstrated to outperform hydroxychloroquine and cannabidiol for anti-inflammatory properties in a pre-clinical *in vivo* study

Highlights:

- Results from an *in vivo* model of rheumatoid arthritis indicate that IHL-675A has a benefit in the treatment of rheumatoid arthritis greater than that of CBD or HCQ alone
- HCQ is approved and widely used for treatment of rheumatoid arthritis in the form of hydroxychloroquine sulphate; marketed as Plaquenil
- Low dose IHL-675A was 1.06 to 3.52x more effective at reducing arthritis across multiple assessments including clinical score, paw volume, pannus score, total histology score and serum cytokine levels as the standard dose of HCQ
- Results demonstrate that IHL-675A, which combines CBD and HCQ, has the potential to permit a ten-fold reduction in HCQ dose, without sacrificing efficacy, in treatment of arthritis
- Potential reduction in HCQ dosage for a similar efficacy outcome may entail lower side effect profile for patients treated with HCQ
- Incannex to launch a sixth clinical program to target rheumatoid arthritis, which has a global addressable treatment market of US$57B per annum.

Clinical stage pharmaceutical development company, Incannex Healthcare Limited (ASX: IHL, 'Incannex' or the 'Company'), is pleased to announce that it has received positive results from another *in vivo* (animal) study that has further assessed the anti-inflammatory capability of its proprietary IHL-675A, which is a drug that combines cannabidiol ('CBD') and hydroxychloroquine ('HCQ'). These results have triggered the launch of a sixth clinical program to target Rheumatoid Arthritis ('RA'); a new indication for Incannex with a global yearly addressable market size of more than US$57B[(1)].

Incannex has demonstrated the potent anti-inflammatory activity of IHL-675A in both *in vivo* and *in vitro* studies; making it an excellent candidate for prevention and treatment of inflammatory conditions, including lung inflammatory conditions, such as sepsis associated acute respiratory distress syndrome ('SAARDS'), COPD, asthma and bronchitis. On the 16th of February, the Company also outlined more pre-clinical results from the IHL-675A research program which demonstrated that IHL-675A was more effective at treating colitis, a form of inflammatory bowel disease, than CBD alone.

Incannex's discovery that CBD and HCQ display strong synergistic anti-inflammatory activity increased the potential for IHL-675A beyond these conditions and into other inflammatory indications. To further assess the therapeutic potential of IHL-675A in inflammatory diseases, a rat model of arthritis was employed.

Overview

In this model, female Lewis rats were challenged with porcine type-II collagen with Freund's adjuvant on Day 1 (0.2 mg/0.2 mL/rat) by subcutaneous injection at the base of the tail to induce arthritis. A booster injection at 0.1 mg/0.1 mL/rat was injected on Day 7. On day 16, rats were allocated into groups of six.

There were ten groups of modelled rats and one sham injected group. CBD, HCQ or the combination of CBD and HCQ (IHL-675A) were injected intraperitoneally once per day from day 17 to 30 (total of 14 days). Drug doses were 1 and 10 mg/kg CBD and 2.5 and 25 mg/kg HCQ.

The 10 mg/kg CBD and 25 mg/kg HCQ doses were selected as they are representative of standard doses in humans based on the FDA body surface area dose equivalence estimation for rats to humans of 6/37[(2)]. For a 60 kg person, the 10 mg/kg CBD dose in rats is equivalent to 97 mg and the 25 mg/kg HCQ dose in rats is equivalent to 243 mg. The maintenance dose range recommended for rheumatoid arthritis in the Plaquenil prescribing information is 200-400 mg daily[(3)].

Disease was assessed by measuring hind paw volume with a plethysmometer and using a qualitative severity score system as outlined in **Appendix 1, Table 1** on days 1, 7 ,10, 14, 16, 18, 20, 22, 24, 26, 28 and 30.

Post termination on day 30, blood was collected from all rats and analysed for levels of the inflammatory cytokines IL-1β and IL-6 using commercially available ELISA kits. These two cytokines were selected as they are known to be involved in the pathophysiology of rheumatoid arthritis[(4)]. Both hind paws were harvested, weighed and formalin-fixed for histopathology. Histopathological evaluation consisted of an evaluation of cartilage and bone destruction by pannus formation (an abnormal layer of fibrovascular or granulated tissue) and mononuclear cell infiltration in synovial joint tissues according to the scoring matrices presented in **Appendix 1, Tables 2 and 3**. A total histology score, which is a sum of the pannus formation and mononuclear cell infiltration scores, was also calculated. For all assessments, the score was sham subtracted and then the reduction relative to the vehicle group was calculated.

Results

IHL-675A outperformed CBD and HCQ alone (at equivalent doses) at reducing clinical score and paw volume at days 24 and 30, pannus formation, total histology score, IL-1β and IL-6 in a rat model of arthritis. The reduction in disease assessments by IHL-675A was 1.07-8.72 times that observed for HCQ

alone at an equivalent dose (**Figure 1**, **Appendix 1, Table 4**). This indicates that IHL-675A has a benefit in a rat model of arthritis greater than that of CBD or HCQ alone. In turn, this means that there is potential for IHL-675A in treatment of arthritis in humans.

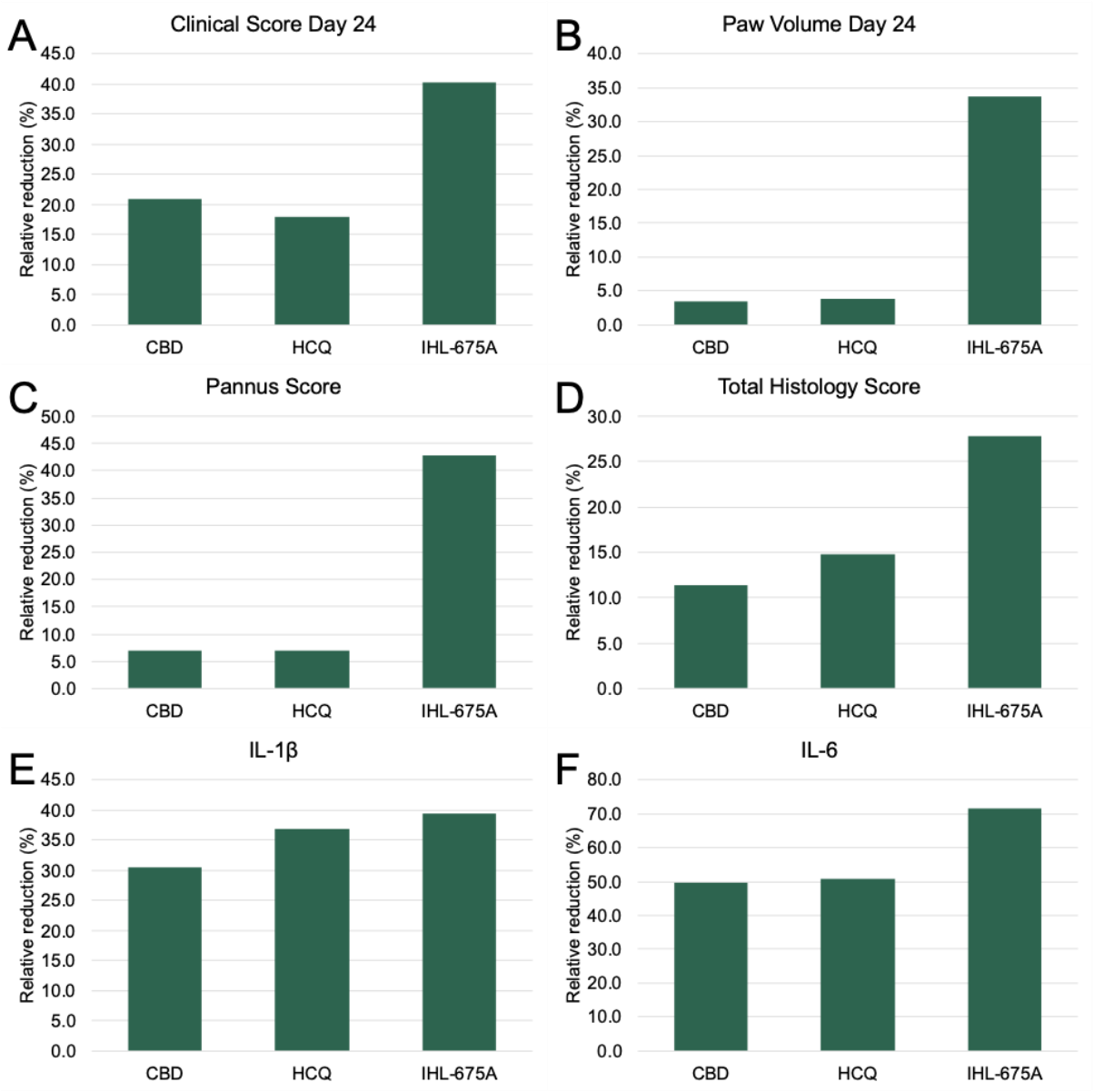


Figure 1. Comparison of IHL-675A to its component drugs CBD and HCQ in reduction of disease assessments in a rat model of rheumatoid arthritis. *Groups of rats that had undergone collagen-induced arthritis modelling were treated with IHL-675A, CBD or HCQ at equivalent doses. The reduction in arthritis disease severity in IHL-675A treated rats was greater than for either CBD or HCQ treated rats with respect to (A)*

clinical score at day 24, (B) paw volume at day 24, (C) pannus formation, (D) total histology score, (E) serum IL-1β levels and (F) serum IL-6 levels.

HCQ is approved for treatment of rheumatoid arthritis in the form of hydroxychloroquine sulphate and marketed as Plaquenil[5]. Hydroxychloroquine has known risks for ocular toxicity and cardiac effects including cardiomyopathy and QT prolongation, as listed in the prescribing material. The most important predictor of retinal toxicity is the cumulative dose of HCQ[6].

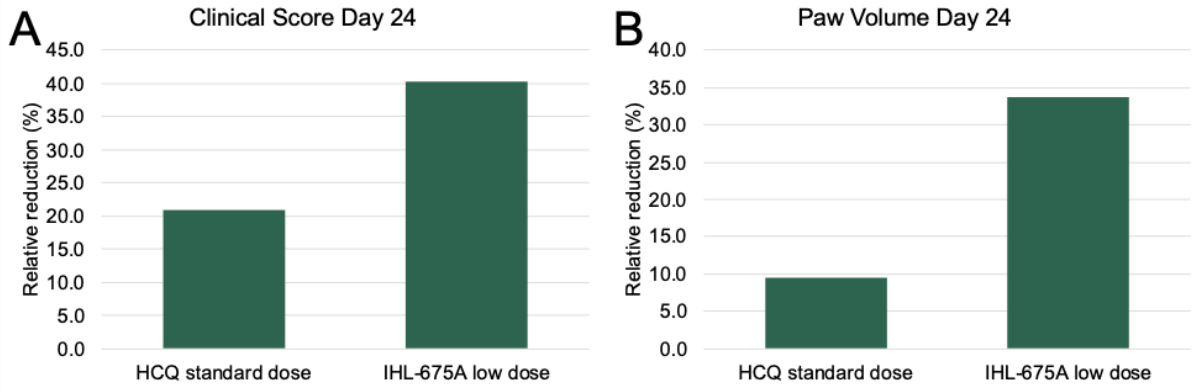
Similarly, long term use of HCQ in rheumatoid arthritis patients was associated with increased cardiovascular mortality[7]. Therefore, there is significant value in reducing the dose of HCQ in these arthritis patients. To understand the capacity for the combination of CBD with HCQ to permit reduction of the HCQ dose, low dose IHL-675A (1 mg/kg CBD + 2.5 mg/kg HCQ) was compared to a standard dose of HCQ (25 mg/kg HCQ). The 25 mg/kg HCQ dose in rats is equivalent to a 243 mg HCQ dose in a 60 kg human based on the FDA body surface area dose equivalence of 6/37.

Low dose IHL-675A was more effective at reducing arthritis across multiple assessments including clinical score, paw volume, pannus score, total histology score and serum cytokine levels than the standard dose of HCQ. The reduction in disease assessments by low dose IHL-675A was 1.06-3.52 times that observed for HCQ alone at the standard dose (**Figure 2**, **Appendix 1, Table 5**).

This indicates that the combination of CBD and HCQ in IHL-675A has the potential to permit a ten-fold reduction in HCQ dose, when combined with CBD, without sacrificing efficacy in treatment of arthritis.

Incannex has broadened claims within initial patent filings to cover rheumatoid arthritis as an indication. IHL is continuously monitoring the results of its research and development program, with a view to identifying and protecting new IP that aligns with its commercial objectives.

By taking a global approach to its IP strategy, IHL intends to pursue patent protection in key global markets, including the US, Europe, Japan and Israel. To this end, IHL has filed an International Patent Application (PCT application) to pursue aspects of the therapeutic use of IHL-675A products. This approach aligns with IHLs regulatory strategy, including the submission of a pre-IND meeting request to the US Food and Drug Administration ('FDA') for IHL-675A products.



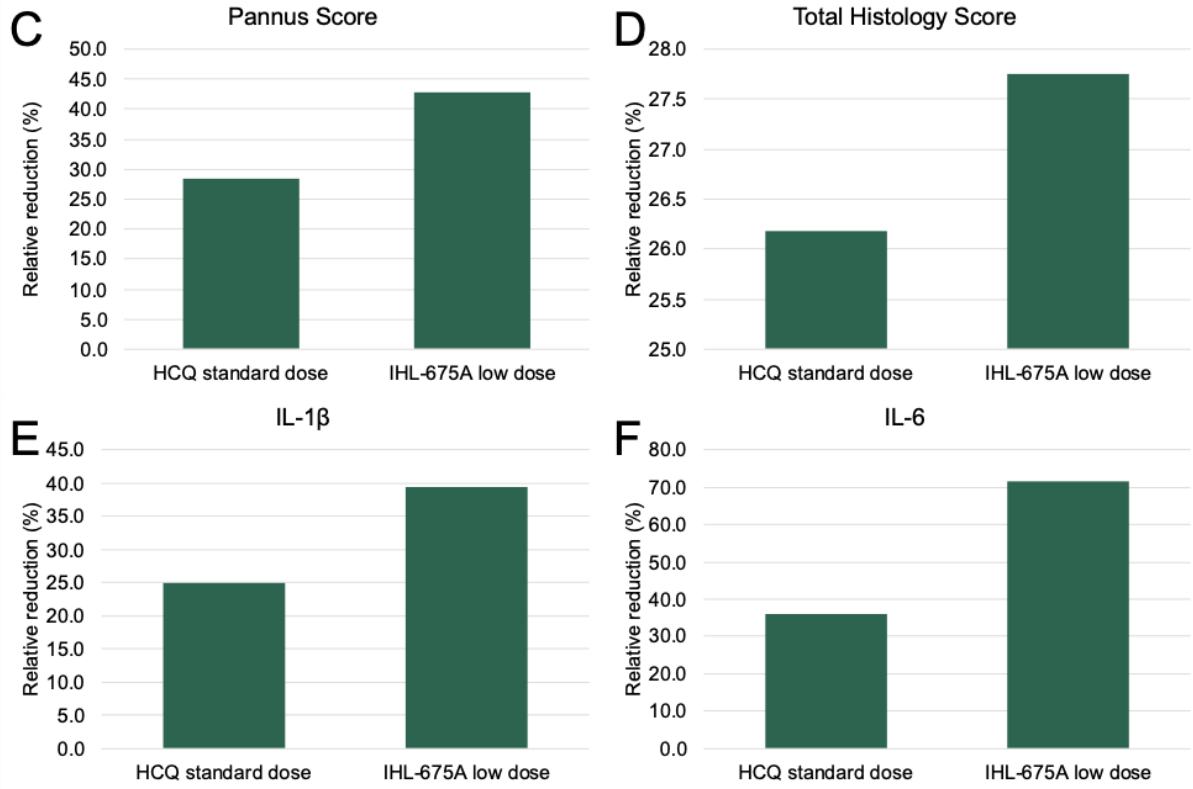


Figure 2. Comparison of low dose IHL-675A and standard dose HCQ in reduction of disease assessments in a rat model of rheumatoid arthritis. *Groups of rats that had undergone collagen-induced arthritis modelling were treated with low dose IHL-675A (1 mg/kg CBD + 2.5 mg/kg HCQ) or standard dose HCQ (25 mg/kg HCQ). The reduction in arthritis disease severity in low dose IHL-675A treated rats was greater than for standard dose HCQ treated rats with respect to (A) clinical score at day 24, (B) paw volume at day 24, (C) pannus formation, (D) total histology score, (E) serum IL-1β levels and (F) serum IL-6 levels.*

CEO and Managing Director of Incannex Healthcare, Mr Joel Latham said;

"Incannex is delighted with the results from this study. Hydroxychloroquine is an established medication for rheumatoid arthritis and IHL-675A has been demonstrated to outperform it at reducing disease severity in an animal model.

The benefit of the CBD and hydroxychloroquine combination in IHL-675A is potent. The observation that IHL-675A was as effective or better than a standard dose of hydroxychloroquine, even though it contained 90% less drug, is an exciting result for the Company. It indicates that IHL-675A has the potential to be a breakthrough in the treatment of rheumatoid arthritis in humans. Therefore, the company is rigorously working with its scientific team and advisors to arrange the next steps to advance

IHL-675A for use in patients with rheumatoid arthritis. We will advise ASX of these plans once they are formalised".

About Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory disorder that can affect more than just your joints. In some people, the condition can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels.

An autoimmune disorder, rheumatoid arthritis occurs when your immune system mistakenly attacks your own body's tissues. Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of your joints, causing a painful swelling that can eventually result in bone erosion and joint deformity.

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:

Mr Joel Latham, Managing Director and Chief Executive Officer
P: +61 409 840 786
E: joel@incannex.com.au

References:

(1) https://www.alliedmarketresearch.com/rheumatoid-arthritis-RA-drugs-market#:~:text=The%20global%20rheumatoid%20arthritis%20drugs,pain%20and%20inflammation%20in%20joints.
(2) https://www.fda.gov/media/72309/download
(3) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
(4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3383508/, https://pubmed.ncbi.nlm.nih.gov/15150426/
(5) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
(6) Wolfe F, Marmor MF. 2010. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken) 62:775–784.
(7) Lane JCE, Weaver J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H, Alser O, Alshammari TM, Biedermann P, Banda JM. 2020. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. Lancet Rheumatol 2:e698–e711.

About Incannex Healthcare Limited (ASX: IHL)

Incannex Healthcare Limited (IHL.ASX) is a clinical stage pharmaceutical development company developing unique medicinal cannabis pharmaceutical products and psychedelic medicine therapies for the treatment of Generalised Anxiety Disorder (GAD), Obstructive Sleep Apnoea (OSA), Traumatic Brain Injury (TBI)/Concussion and Acute Respiratory Distress Syndrome (ARDS). FDA registration, subject to ongoing clinical success, is being pursued for each product and therapy under development.

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

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 and therapies 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 Incannex.

Website: www.incannex.com.au

Investors: investors@incannex.com.au

Appendix 1

Table 1. Disease severity score matrix

Score	Condition
0	Normal
1	Mild, but definite redness and swelling of the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits
2	Moderate redness and swelling of ankle of wrist
3	Severe redness and swelling of the entire paw including digits
4	Maximally inflamed limb with involvement of multiple joints

Table 2. Cartilage and bone destruction by pannus formation scoring matrix

Score	Condition
0	no change
1	Mild change- pannus formation within cartilage
2	Moderate change- pannus invasion into cartilage/subchondral bone
3	Severe change- pannus invasion into the subchondral bone

Table 3. Mononuclear cell infiltration scoring matrix

Score	Condition
0	no infiltration
1	Mild infiltration
2	Moderate infiltration
3	Severe infiltration

Table 4. Comparison of IHL-675A with CBD and HCQ alone at equivalent doses at reducing disease assessments in a rat model of arthritis. Values are percentage reductions relative to the vehicle.

	CBD	HCQ	IHL-675A	IHL-675A vs HCQ*
Clinical Score Day 24	20.9	17.9	40.3	2.25
Clinical Day 30	17.1	24.3	31.4	1.29
Paw Volume Day 24	3.6	3.9	33.7	8.72
Paw Day 30	17.5	8.0	23.4	2.94
Pannus Score	6.9	6.9	42.9	6.25
Total Histology Score	11.4	14.8	27.8	1.88
IL-1β	30.5	36.9	39.3	1.07
IL-6	49.6	50.9	71.6	1.40

***IHL-675A score relative to HCQ**

Table 5. Comparison of low dose IHL-675A with standard dose HCQ at reducing disease assessments in a rat model of arthritis. Values are a percentage reduction relative to the vehicle.

	HCQ standard dose	IHL-675A low dose	Low dose IHL-675A vs Standard dose HCQ*
Clinical Score Day 24	20.9	40.3	1.93
Clinical Day 30	25.7	31.4	1.22
Paw Volume Day 24	9.6	33.7	3.52
Paw Day 30	20.4	23.4	1.15
Pannus Score	28.3	42.9	1.52
Total Histology Score	26.2	27.8	1.06
IL-1β	24.8	39.3	1.58
IL-6	35.9	71.6	2.00

***IHL-675A low dose relative to HCQ standard dose**