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In-Vitro Study Confirms Effectiveness of ArtemiC on Human Immune Cells to Inflammatory Stimuli

ASX RELEASE

Key Highlights:

- A final report of results from preclinical in-vitro laboratory testing clearly support the claim that ArtemiC can modify the function of human immune cells in response to inflammatory stimuli
- Specifically, some elements of the formulation demonstrated an effective response on immune function in a manner considered desirable in the treatment of COVID-19
- The combination of the ArtemiC ingredients consisting of Artemisinin, Curcumin, Boswellia serrata, and Vitamin C, demonstrated an enhanced effect as compared to the separate agents
- These findings support the clinical study hypothesis that ArtemiC can have a beneficial impact on the malignant "Cytokine Storm" which plays an important role in the clinical deterioration of those severely affected by infection with the CoV-SARS-2 virus

MGC Pharmaceuticals Ltd (ASX: MXC, 'MGC Pharma' or 'the Company'), a European based bio-pharma company specialising in the production and development of phytocannabinoid-derived medicines, is pleased to announce results from pre-clinical in-vitro laboratory tests which have shown effective immunological activity for the use of ArtemiC as an immune-modulatory agent for the treatment of COVID-19 ("**Study**").

The in vitro immunological evaluations were conducted by independent clinical research laboratory, MyPlant Bio, Israel. The Study was a preclinical in vitro immunological evaluation of the micellized-formulations and were designed to test the effect of ArtemiC and its ingredients (consisting of Artemisinin, Vitamin C, Curcumin, Boswellia serrata) on responses of human Peripheral Blood Mononuclear Cells (PBMCs) to inflammatory stimuli.

The evaluation was conducted in a model serving the study of the Cytokine Storm Syndrome, a model noted by the FDA to be a good predictor for cytokine storm response and immunotoxicity. When the production of cytokines is excessive and uncontrolled it is described as a "Cytokine Storm". This phenomenon occurs due to failure to contain the body's reaction to stimuli that occur in response to infection. The severe clinical deterioration due to COVID-19 is attributed to a significant degree to these circumstances of Cytokine Storm and serves a representative example of the fatal consequences that such a failure may entail.

Immunology In-vitro Study Results

The Study results indicate that ArtemiC can reduce the risk of inflammation by diminishing the release of the interleukins (IL-1β and IL-6) from PBMCs in response to standard stimulation by exposure to Lipopolysaccharide (LPS). Interleukins trigger inflammation and modulate the immune response, and Lipopolysaccharide (LPS) is an agent that causes the production of cytokines that leads to cytokines storm.

These results are considered particularly important by the Company and its clinical research team as IL-6 has been implicated in the exacerbation of COVID-19 clinical deterioration.

The research data suggests that the combination of the active ingredients of ArtemiC is more potent and does elicit an in-vitro effect on immunological response during a disease.

IL-2 interleukin is a central driving force in the immune response and high levels of pro-inflammatory cytokines are in direct correlation with the disease severity.

Further studies are underway and planned to augment these initial findings to evaluate the preferable ratios between the active ingredients.

Importance of Pre-Clinical Study Results Data and Phase II Clinical Trial Interim Results

According to the general FDA requirements for the pharma industry and guidelines published especially for COVID-19 studies, MGC Pharma is currently managing preclinical studies in parallel to the Phase IIa clinical trial. The focus of the preclinical program is to demonstrate the safety, toxicity and mechanism of action of ArtemiC as a drug for COVID-19 infection. All information will be obtained in these trials, will serve the Company to design Phase IIb and Phase III studies. Study procedures and endpoints will be defined based on the preclinical studies and Phase IIa results. In addition, the toxicity study results recently published support the definition of maximum tolerated dose and dose finding process, which will be required as a part of the R&D process by the regulatory authorities.

The Company is currently awaiting the first interim results from the COVID-19 infected patients from the Phase II randomised, double blind clinical trial underway in Israel, which are expected to be finalised shortly.

Current clinical evidence in COVID-19 patients indicate that the Cytokine Storm is an uncontrolled over-production of soluble markers of inflammation which, in turn, sustain a systemic inflammatory response, and is a major factor responsible for the occurrence of Acute Respiratory Distress Syndrome – the main mortality reason in COVID-19 patients. ArtemiC is currently being tested in a clinical trial where some of the participants may be affected by a cytokine storm, with interim patient statistical analysis of the Phase IIa clinical trial part of the data expected to be received shortly by the Company.

Roby Zomer, Co-founder and Managing Director of MGC Pharma, commented: "We are very pleased to have achieved these results, which have been completed in line with FDA requirements for COVID-19 studies and provide important data points for our Phase IIb and III trial design and protocols."

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About MGC Pharma

MGC Pharmaceuticals Ltd (ASX: MXC) is a European based bio-pharma company developing and supplying affordable standardised phytocannabinoid derived medicines to patients globally. The Company's founders were key figures in the global medical cannabis industry and the core business strategy is to develop and supply high quality phytocannabinoid derived medicines for the growing demand in the medical markets in Europe, North America and Australasia. MGC Pharma has a robust product offering targeting two widespread medical conditions – epilepsy and dementia – and has further products in the development pipeline.

Employing its 'Nature to Medicine' strategy, MGC Pharma has partnered with renowned institutions and academia to optimise cultivation and the development of targeted phytocannabinoid derived medicines products prior to production in the Company's EU-GMP Certified manufacturing facility.

MGC Pharma has a number of research collaborations with world renowned academic institutions, and including recent research highlighting the positive impact of using specific phytocannabinoid formulations developed by MGC Pharma in the treatment of glioblastoma, the most aggressive and so far therapeutically resistant primary brain tumour.

MGC Pharma has a growing patient base in Australia, the UK, Brazil and Ireland and has a global distribution footprint via an extensive network of commercial partners meaning that it is poised to supply the global market.

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ANNEXURE A

Study Design:

A preclinical in vitro immunological evaluation of the micellized-formulations was performed by MyPlant Bio for MGC Pharma. The formulations were tested in in-vitro assays measuring the effect on immune responses. These assays included a) in-vitro cytotoxicity assay; b) Cytokine secretion assays that was performed in in-vitro and not under actual cytokine storm conditions. The main goal of these experiments was to evaluate the inhibitory effect of the formulations on the inflammatory response of human PBMCs.

The inflammatory response is a central component of the immune response against pathogens. White blood cells use a set of sensors to recognize the pathogen and produce cytokines in response. These cytokines trigger inflammation and recruit other cells of the immune system for help. Cytokines, such as interleukin-1b (IL-1β), IL-6 and IL-2 trigger inflammation, modulate the immune response and act as endogenous pyrogens. When the production of cytokines is excessive and uncontrolled it is described as a "Cytokine storm". The body struggles to regain control and regulate the response. However, when cells fail to terminate the inflammatory response the cytokine storm may have irreversible consequences. MyPlant-Bio's Cytokine Storm Assay is a well-established preclinical in-vitro (or practically exvivo) assay. It provides evaluation of Cytokine Storm Syndrome using human peripheral blood mononuclear cells (hPBMCs). The FDA considers this assay as a good predictor for cytokine storm response and immunotoxicity, and it is commonly required in the development of biological treatments. The Cytokine Storm Assay evaluates the inhibitory effect of test items on cytokine secretion by human PBMCs, in response to bacterial Lipopolysaccharides (LPS - a cytokine storm inducing agent).

The study was performed on commercial human Peripheral Blood Mononuclear Cells (PBMC) sourced from a healthy donor. Exposue time was 24 hours.

Study groups:

- Micellized-Artemisinin
- Micellized -Olibanum
- Micellized -Vitamin C
- Micellized -Curcuma
- Micellized -ArtemiC (mix formulation)

24 assays were perfomed during the experiment. Assays were performed for each one of the components as well as the combination and controls for comparison. The assays were performed in triplicate for each element. Separate assays were performed with two forms of stimulation of the immune cells – One set of tests with LPS (lipopolysaccharide) which was performed twice, and another set with T-Cell Receptor (TCR) stimulation by means of anti-CD3 and anti-CD28 antibodies. The immunologic assay included evaluation of the effect of the test compounds (in different concentrations) on the in vitro cytotoxicity and cytokine production. Experiments were conducted on commercial human immune Peripheral Blood Mononuclear Cells (PBMCs) from heathy donors.

As noted, , treatments of COVID-19 by reducing the excessive dysregulation activation of the immune system are being referenced the excessive dysregulated activation of the immune system ("cytokine storm) described in COVID-19 is the object of intervention with ArtemiC. Curcumin, Artemisinin C, Olibanum and decreased the secretion of cytokines (IL-1β and IL-6, IL-2) from human blood cells which mediate immune functions and are recognized as a model for the immune function which is useful in the study of the Cytokine Storm. The said diminishing of cytokine secretion is the "desirable" effect relevant to the management of COVID-19. The combination of all the elements in the ArtemiC formulation was noted to enhance the desirable effect, which supports the scientific basis of the mechanism of action of ArtemiC as an anti-inflammatory drug that can reduce the cytokine storm, one of the mail, reasons for mortality in COVID-19 patients. Clinical intervention in patients with corona virus disease 2019 (COVID-19) has demonstrated a strong upregulation of cytokine production in patients who are critically ill with SARS-CoV2-induced pneumonia (X. Sun et al., Cytokine storm intervention in the early stages of COVID-19 pneumonia, Cytokine Growth Factor Rev. 2020 Jun;53:38-42.).

Based on the published scientific papers, once immunologic complications like cytokine storm occur, anti-viral treatment alone is not enough and should be combined with appropriate anti-inflammatory treatment (M. Soy et al., Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment, Clinical Reumathology, 2020 May 30 : 1–10). Based on the in vitro results, our suggestsion that the mechanism of action of ArtemiC is focused on the anti inflammatory effect that reduces the cytokines production and prevents cytokine storm in COVID-19 patients.

The cytotoxicity assays were performed in preparation to establish the technique and identify the concentration that could be used without impacting the viability of the cells (clearly if the cells are not viable, they will not produce and secrete the cytokines). In the reported experiments testing the cytokine levels the cell viability was test in parallel to verify the changes in cytokine levels could not be attributed to death of the cells.

Study Results:

- The cytotoxicity assay revealed that each stock micelle-formulation has a different cytotoxic limit. The maximal non-cytotoxic concentrations were chosen: Artemisinin - 1µg/ml, Vitamin C - 5µg/ml, Olibanum – 1.3µg/ml and Curcumin - 3µg/ml.
- Results of the LPS-induced cytokine secretion immunological assay show that formulations of ArtemiC, Micellized-Curcumin and Micellized-artemisinin had an inhibitory effect on the secretion of pro-inflammatory cytokines without significantly compromising cell viability. The mixture of these four compounds was more effective than each compound alone, implying additive effect of the compound combination
- Results of the T – cell receptor activation-induced cytokine secretion assay show that Curcumin had an inhibitory effect on IL-2 secretion.

The control test with LPS and no addition of active ingredients yielded a concentration of 2335 pg/ml of IL-1β in the medium.
The test with curcumin at a concentration of 1.5µg/ml yielded a concentration of 1678 pg/ml of IL-1β in the medium.
The test with artemisinin at a concentration of 0.5µg/ml yielded a concentration of 889 pg/ml of IL-1β in the medium.
The test with Olibanum at a concentration of 0.625µg/ml yielded a concentration of 1822 pg/ml of IL-1β in the medium.

The test with the ArtemiC combination with concentrations of the ingredients identical to those reported above – including artemisinin at a concentration of 0.5µg/ml + curcumin 1.5µg/ml, Olibanum 0.625µg/ml and Vit C 2.5µg/ml yielded a concentration of 553 pg/ml of IL-1β. The differences between the concentrations were distinct and consistent in all the wells. The numbers are small to the extent that statistical extrapolation is not justified. However, the differences are distinct that demonstrates a clear vector of the results. Further experiments will provide further data for analysis. These results are presented in Fig 1.

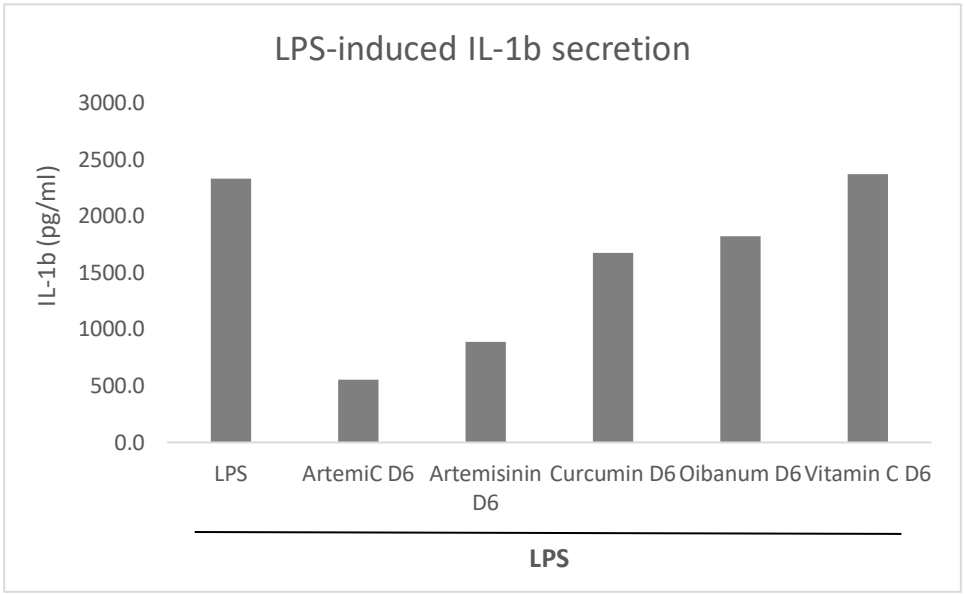


Fig 1. LPS-induces IL-1b secretion

Additional data is presented in Table 2, including IL-1 secretion.

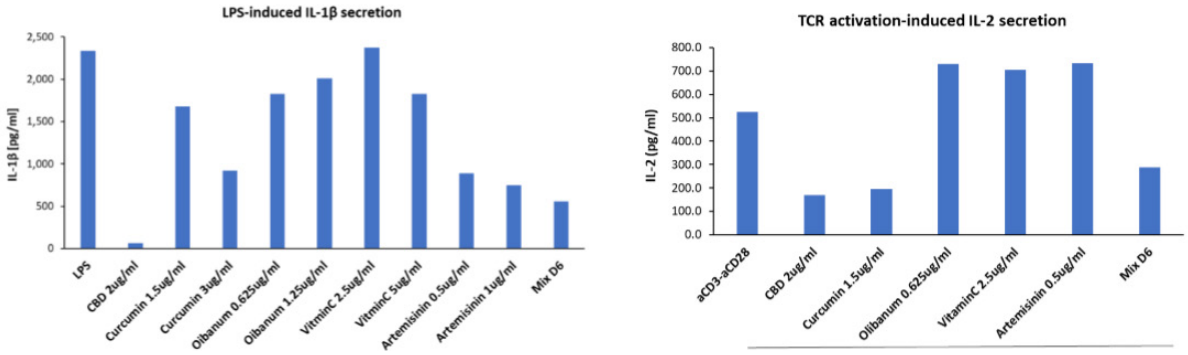


Fig 2. LPS-induced IL-1 and IL-2 secretion.

The cytotoxicity assay results present the percent of the dead cells in the experimental tissue. The results are presented in Fig. 3.

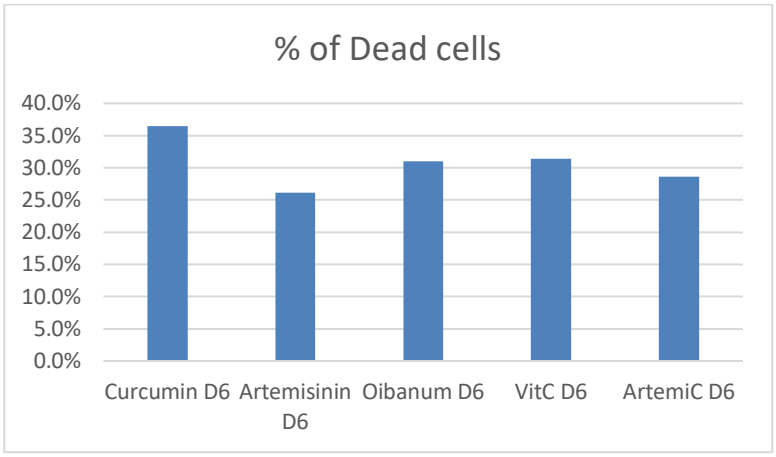
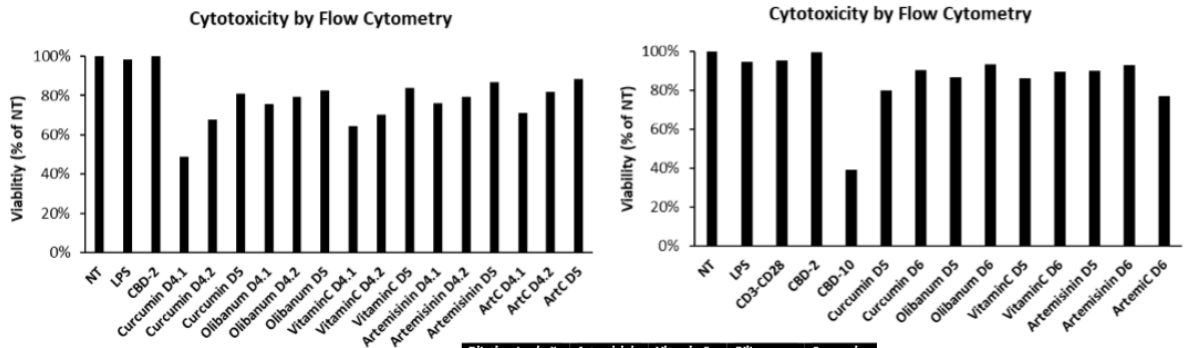


Fig 3. Cytotoxicity assays results.



Dilution (µg/ml)	Artemisinin	Vitamin C	Olibanum	Curcumin
D4.1	4	20	5	12
D4.2	2	10	2.5	6
D5	1	5	1.25	3
D6	0.5	2.5	0.625	1.5

Fig 4. Cytotoxicity by Flow Cytometry

Due to the urgent introduction of ArtemiC into a clinical trial we deemed it necessary to substantiate the existing knowledge on its ingredients and partial combination with testing to verify the immune-regulatory activity of the full combination in its unique micellar formulation. Further testing is aimed at further justifying and adjusting the use of the ingredients and the ratio between them – after the initial introduction of a preparation that was readily available and in use in a different capacity. Immunological testing is crucial for the Phase IIb and III studies design. The anti inflammatory mechanism of action of ArtemiC, proven in vitro, will lead the Company to design the future phases focused on the immunological response and not only clinical improvement. In addition, study endpoints and procedures will be defined with the focus on the cytokines production and ArtemiC ability to affect it.