17 April 2020

ASX Code: MXC

Ethics Committee Approval Received for Phase II Clinical Trial on Patients Diagnosed with COVID-19

MGC Pharmaceuticals Ltd (ASX: MXC, 'MGC' or 'the Company'), a European based 'Seed to Medicine' bio-pharma company specialising in the production and development of phytocannabinoid-derived medicines, is pleased to announce it has been granted Human Research Ethics Committee ('**Ethics Committee**') approval from Nazareth Hospital EMMS in Israel to conduct a Phase II placebo controlled clinical trial to evaluate the safety and efficacy of a natural anti-infective based formulation ('**ArtemiC**' or the '**Product**') on patients diagnosed with COVID-19 (the '**Trial**').

As detailed in the announcement released 15 April 2020, the Company entered into a binding agreement with Micelle Technology AG ('**Micelle**'), the parent company of Swiss PharmaCan AG (together the '**Parties**'), on 4 April 2020 for MGC to provide necessary research support, commercial manufacturing and distribution of the Product, now named ArtemiC. This clinical trial is being undertaken pursuant to the terms of the executed binding agreement, with MGC the responsible party for the design and management of future clinical studies on the Product as outlined in the key terms of the agreement in the announcement of 15 April 2020. The Product is based on the Parties' patented[1] MyCell Enhanced™ delivery system technology ('**MyCell™**').

Highlights

- MGC has received Ethics Committee approval from Nazareth Hospital EMMS in Israel for a Phase II clinical trial to be undertaken on patients diagnosed with COVID-19
- Approved as "Special Clinical Trial" there is no requirement for any additional approval from the Israeli Ministry of Health to commence the Trial
- ArtemiC is designed with the scientific aim to target viral infections with inflammatory complications, and is now to be evaluated on novel coronavirus 2019 (SARS-CoV-2) infected patients in a double-blind placebo controlled, Phase II clinical trial
- The Trial will evaluate the safety and efficacy of ArtemiC in the treatment of patients diagnosed with COVID-19
- The Trial is expected to commence in April 2020, and conclude in September 2020 with results available October 2020
- Micelle holds the exclusive right to the award-winning[2] and patented MyCell™ delivery system technology that is used in the formulation of ArtemiC
- MyCell™ technology is a unique platform to deliver natural ingredients more effectively in higher concentrations to the cells, improving bioavailability of natural ingredients

The Ethics Committee approval for a Phase II clinical trial on patients diagnosed with COVID-19 follows the successful completion of a full ethical review undertaken by Human Research Ethics Committee at the Nazareth Hospital EMMS, Israel. ArtemiC is a natural supplement formula based on Artemisinin and Curcumin (along with supporting ingredients Vitamin C and Boswellia serrata) well-known natural active ingredients with anti-infective properties (see Annexure A).

Rationale for Clinical Program

The scientific and clinical teams in both Micelle and MGC commenced planning for new testing programs to evaluate ArtemiC further potential to treat different anti-infective, anti-viral and anti-inflammatory indications, including patients infected with COVID-19.

[1] Patent number: EP2066310A1 granted on 18 April 2012

[2] 2018 Award - Excellence in Pharma: Formulation by MiVital AG (part of the Micelle group of companies)

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MGC's Clinical Advisory Team, led by Dr Jonathan Grunfeld and Dr Nadya Lisovoder, evaluated and concluded the established scientific data of known Artemisinin and Curcumin properties provide a rationale to test ArtemiC in the treatment of patients suffering from COVID-19 as detailed in Annexure A, and a basis to undertake this further testing on ArtemiC.

ArtemiC is currently designated as a food supplement. As detailed in the announcement dated 15 April 2020, MGC is responsible for the necessary research, manufacture and packaging for commercial orders from its EU GMP facility in Slovenia. This opportunity will not impact MGC's current operations or the production and delivery of its leading phytocannabinoid based medicines – (including CannEpil® and CogniCann®).

Phase II Clinical Trial

The Phase II Trial which has been approved by the Ethics Committee from Nazareth Hospital EMMS is designed to test ArtemiC on patients infected with COVID-19 for safety and efficacy, with the purpose of treating the pathophysiological repercussions of infection with the novel coronavirus 2019 (SARS-CoV-19). The protocols for this Trial were finalised by the MGC Clinical Advisory Team, led by Dr Grunfeld and Dr Lisovoder, and provided to the Ethics Committee for approval, which has now been received. Due to the definition of the Trial being a "Special Clinical Trial", there is no requirement for any additional approval from the Israeli Ministry of Health to commence the Trial.

The Trial is expected to commence in April 2020, following placement of clinical trial insurance, on a target number of 50 patients infected with COVID-19. The Trial will be conducted over a period of 14 days per patient and is expected to conclude September 2020, with results available October 2020. Full details on the Phase II clinical trial required for compliance with the ASX Code of Best Practice for Reporting by Life Science Companies are included in Annexure B. A successful outcome from a clinical trial does not necessarily guarantee regulatory approval of ArtemiC.

In the event of a successful Trial on patients diagnosed with COVID-19, MGC and the Parties would make a decision based on the results for additional clinical programs on ArtemiC with the ultimate aim to achieve full marketing authorisation through the completion of additional successful clinical trials. If the Trial is not successful, the Company would examine the results and decide at that time on the potential to proceed with further testing on ArtemiC.

Roby Zomer, Co-founder and Managing Director of MGC Pharmaceuticals, commented: "Following our recently announced agreement with Micelle, this approval to proceed immediately with a Phase II clinical trial of ArtemiC is a major milestone. This trial will evaluate the safety and efficacy of ArtemiC on patients diagnosed with COVID-19 and we look forward to updating the market with developments."

--Ends--

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About MGC Pharma

MGC Pharmaceuticals Ltd (ASX: MXC, OTCQB: MGCLF) 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 'Seed 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 recent research conducted in collaboration with the National Institute of Biology and University Medical Centre Ljubljana, highlighted the positive impact of using specific phytocannabinoid formulations 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. In order to meet the demands of becoming a key global supplier the company is constructing a large scale GMP state of the art facility in Malta.

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About Nazareth Hospital EMMS

The Nazareth Hospital EMMS is one of the oldest hospitals in the Middle East, and the largest in Nazareth. The hospital started its mission in Nazareth 156 years ago by Dr. Vartan, and gradually expanded. The hospital serves the population of Nazareth and the surrounding area. Today it is a general hospital with Nazareth's main Emergency Room that works 24/7, ICU, a recently refurbished Cath Lab, Orthopaedic Surgical department, General Surgical department, Pediatric surgical unit, Urology Unit and Esthetic Clinic. It also has a Medical department with its services: Tuberculosis and Cardiac clinics. The hospital also has a Dialysis unit, Psychiatry Department, Delivery rooms, a unique Neonate unit, Gastrology unit, X-ray department and other medical clinics that serve tens of thousands of patients every year.

The hospital is affiliated with Bar-Ilan University and is committed to the development of medical education and research. Each year the hospital has many students of medicine, nursing and other medical fields from universities and colleges from Israel and around the world. It is one of the area's biggest employers and seeks to serve all the people in the area, with the highest scientific and medical standards.

ANNEXURE A

Rationale for Studying the Micellar Formulation ArtemiC in the Treatment of COVID 19

An outbreak of pneumonia in December 2019, in Wuhan city, China (Tan, Zhao et al.), heralded the outbreak of a rampant epidemic that has caused over 30,000 deaths worldwide within the first three months of 2020 (Coronavirus COVID-19 Global Cases by the (CSSE) at Johns Hopkins University). By the 7th of January 2020 a novel coronavirus, subsequently designated SARS-CoV-2 (Gorbalenya 2020), was identified as the cause of a highly contagious disease known today as coronavirus disease 2019 (COVID-19) (Tan, Zhao et al. , Lu, Zhao et al. 2020, Zhu, Zhang et al. 2020). Prominent clinical and pathophysiological features of the resulting illness include a severe respiratory syndrome with lethal potential (Zhou, Yu et al. 2020), occasional disruption of additional physiological systems (Yang, Yu et al. 2020) potentially leading to a state of shock, including prominent disturbance of immunological function occasionally provoking a cytokine storm (Wong, Lam et al. 2004, Fung, Yuen et al. 2020, Mehta, McAuley et al. 2020), and more. Despite all the efforts made since the surfacing of this disease, no pharmacological therapy has yet been found to be effective in altering its clinical course for the better (Alhazzani, Møller et al. , Dhama, Sharun et al. 2020). This set of circumstances presents a most urgent need to make every possible effort to limit the medical damage caused by COVID-19, as well as the devastating impact the ensuing pandemic has on the communities around the globe (2020).

ArtemiC is a micellar formulation comprising two tested active ingredients, artemisinin and curcumin. These ingredients possess antiviral, antioxidant and anti-inflammatory activities relevant to multiple aspects of the pathophysiology associated with COVID- 19 (Cheng-wei 2001, Dhivya and Rajalakshmi 2017, Efferth 2018). They have been already tested in humans and found to have an amenable safety profile (Chainani-Wu 2003, Medhi, Patyar et al. 2009, Storka, Vcelar et al. 2015). Indeed, there are data from *in vitro* and *in vivo* laboratory studies supportive of the potential of curcumin to be of benefit in the management of viral respiratory distress syndrome (Leitman 2012, Avasarala, Zhang et al. 2013, Guzel, Kanter et al. 2013, Ghandadi and Sahebkar 2017, Lelli, Sahebkar et al. 2017).

This proposal identifies an emergency need for fast tracked clinical studies to address the medical challenges presented by COVID-19. Furthermore, it presents a plan to test the hypothesis that a micellar formulation of the well-studied active ingredients artemisinin and curcumin may be clinically beneficial in the management of the disease.

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Overview

Summary: A preparation of ArtemiC, comprising Artemisinin and Curcumin with the supporting ingredients Boswellia and Vitamin C in a nanoparticular formulation, has been proposed as a treatment for the disease associated with the novel corona virus SARS-CoV-2. This initiative is presented under the urgent circumstances of the fulminant pandemic caused by this lethal disease, which is known as COVID-19 and has spread across the globe causing death and disrupting the normal function of modern society [1]. The grounds for the proposal are rooted in existing knowledge on the components and pharmacological features of this formulation and their relevance to the current understanding of the disease process being addressed.

The Problem: COVID-19 as a lethal disease

The state of emergency associated with the present COVID-19 pandemic has aroused the biomedical community to produce an exceptionally large number of clinical trial proposals [2]. The World Health Organization (WHO) has accordingly addressed the challenge of promoting urgent clinical research on COVID-19 treatment [3] while giving due consideration to the need for rigorous adherence to fundamental ethical requirements [4]. In attempt to render the research efforts more effective an initial Core Outcome Set (COS) for clinical trials in COVID-19 has been developed and published by a Chinese group according to the Core Outcome Measures in Effectiveness Trials (COMET) handbook [5, 6]. Such documents provide guidance in the development of the proposed protocol in conjunction with the constraints due to the extreme circumstances imposed by the pandemic crisis.

Proposed Intervention – Rationale and Selected Comments

Therapeutic approach: Extensive efforts are being made to develop effective treatment for COVID-19, albeit without substantiated success so far [2, 7, 8]. Several strategies are being explored to develop effective therapies for the disease, including research in line with western medicine [2, 8-10], alternatively following traditional Chinese medicine (TCM) [2, 11], and consideration of other parts of herbal medicine [9, 12].
Selected pathogenetic themes: leading factors leading to the severe manifestations of COVID-19, notably the Severe Acute Respiratory Syndrome (SARS), as well as functional deterioration of additional organs and physiological systems, and possibly death, are the focus of the therapeutic intervention suggested in our proposal:

- Perseverance and progression of the viral infection – There is an apparent association between the persistent presence of a high viral load and adverse course of the COVID-19 disease [13, 14]. Thus, any intervention to abort or impede the process of the viral propagation and replication, referred to as antiviral treatment, would appear desirable.
- Dysregulation of the immune system, ultimately manifesting as a “cytokine storm” – This phenomenon has long been associated with acute lung injury, notably in its most severe manifestation as Acute Respiratory Distress Syndrome (ARDS)

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[15-17]. The data on the COVID-19 from the multitude of clinical reports published so far, support a central role for immune dysregulation in giving rise to the severe manifestations of COVID-19 [17-20].

- Oxidative stress – The damaging effect of this factor has been implicated in the pathogenesis of severe lung injury [21] and specifically proposed play a role in the clinical deterioration in patients with COVID-19 [22].

ArtemiC formulation and active ingredients:

General comment – ArtemiC is currently produced and marketed as a natural food supplement comprised of natural active ingredients and formulated in microscopic structures known as micelles. The elements forming the structure of these micelles are in themselves also of exclusively natural origin. The unique formulation is endowed with highly desirable pharmacological features, providing otherwise unattainable high bioavailability to the active ingredients it is designed to deliver.

- Artemisinin – Artemisinin has been identified as an important active ingredient in the Chinese herbal pharmacopeia which gained prominence as an anti-malaria agent following its isolation in 1972 and subsequent characterization [23]. Since then research has revealed additional anti-inflammatory [24, 25], immune-modulatory [26], antioxidant [24] and anti-viral [27-30] qualities of artemisinin that may be of value in coping with COVID-19.
- Curcumin – Curcumin has been isolated from the rhizomes of Curcuma longa (turmeric) over two centuries ago [31], and has been extensively researched by the prevailing scientific methods ever since [32]. An extensive range of biological activities has been discovered over this long period of in the course of investigating the apparent medical qualities with which it has been attributed ever since antiquity [33]. These include anti-cancer [34], anti-bacterial, ant-fungal, anti-viral activities [35], as well as demonstrated antioxidant [36], anti-inflammatory [36, 37], immunomodulatory [38] and cardioprotective capabilities [39-41]
    - Suggestion of efficacy – Worthy of special note with regard to the relevance of ArtemiC to the treatment of COVID-19 are reports of beneficial effects of its active ingredients artemisinin and curcumin on animal models of sepsis [25, 42, 43] and especially in septic acute lung injury [44-47] and other lung injury models [48-50]. The effect of the described interventions with curcumin, artemisinin or one of its derivatives was consistently reflected in the diminished levels of inflammatory cytokines in the blood and the inflamed lungs, as well as the attenuation of inflammatory features in the histopathological examination of the lungs of the actively treated animals as distinct from those treated with placebo [43-45, 48-51]. The apparent benefit from these interventions has also be associated with significantly improved survival [51].
    - Safety in humans – It is commonly accepted that the prevalent clinical use of artemisinin and its derivatives is exceptionally safe [52-57]. Curcumin has also been found very safe to use in human subjects, even in very high doses of formulation designed to enhance its absorption [58, 59] In a review published in 2004 it was noted that no report of artemisinin overdose in patients had been published at the time [55]. A report published in 1998 on the safety of artemisinin and its derivatives surveyed 108 clinical trials which included altogether 9,241 subjects summarized the analysis with the observation that no serious adverse event or severe significant toxicity was reported [54].
    - Pharmacology – Artemisinin is known to be poorly soluble both in water as well as in lipid environments [60]. Upon oral administration artemisinin has been noted to be absorbed incompletely with marked inter-, and intraindividual pharmacokinetic variability [61-65]. Curcumin is also absorbed very poorly when simply ingested without a specific formulation designed to enhance its bioavailability [66, 67]. The constraints placed by undesirable pharmacokinetic features on the exploitation of drugs with highly desirable therapeutic characteristics have been overcome in recent years by the application of a variety of technical modifications of their formulation [68, 69].
    - Since its initial discovery as an anti-malaria agent [70] artemisinin has been shown to be active in multiple contexts [71]. It has been found that artemisinin and its derivatives are active to varying degrees against a variety of parasitic and infectious diseases [27, 71, 72] including possible antiviral activity against coronavirus [73] as well as against cancer cells [74, 75] and immune disorders [76, 77].

      Against this backdrop, research on the effects of artemisinin has associated it with modification of the activity of central cellular signal pathways [78, 79]. Important in the present context are multiple studies on artemisinin and its derivatives that have demonstrated anti-inflammatory and anti-oxidant activities [24, 43, 48, 49, 80] which are relevant to the COVID-19 related pathophysiology as noted above. Thus, for example, treatment with artemisinin and artesunate has been consistently associated with downregulation of IL-6 and TNF-α levels, of NF-κB activity, restriction of inflammatory cell activation and infiltration, as well as other measures of inflammatory response in assorted models, including specifically in models of acute lung injury (ALI) [43, 48, 49, 51, 81]. The upregulation of Heme Oxygenase 1 (HO-1) by artesunate which has been demonstrated in some of these studies [43, 49, 51] is also

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considered highly desirable in the treatment of ALI [82, 83], as well as possibly possessing antiviral activity [84]. It is important to note in the context of the present proposal that these effects have been also observed specifically with artemisinin [81] in addition to the subsequent studies which focused on the effects of artesunate.

- Curcumin has been isolated from the rhizomes of Curcuma longa (turmeric) over two centuries ago [31], and has been extensively researched by the prevailing scientific methods ever since [32]. An extensive range of biological activities has been discovered over this long period of in the course of investigating the apparent medical qualities with which it has been attributed ever since antiquity [33]. These include anti-cancer [34], anti-bacterial, ant-fungal, anti-viral activities [35], as well as demonstrated antioxidant [36], anti-inflammatory [36, 37], immunomodulatory [38] and cardioprotective capabilities [39-41] pertinent to the intervention in the COVID-19 pathogenic processes.
- The treatment suggested in this proposal has the advantage of being readily available as a micellar formulated food supplement. The use of nano-sized micelles make it to circumvent the barriers to the administration of artemisinin with significantly higher bioavailability and pharmacokinetic consistency [85, 86]. In addition, micellar structures have noted to have improved access to the sites of inflammation associated with increased permeability [68], as expected in conditions of acute lung injury of the nature encountered in COVID-19 pneumonia [87]. Combining these novel improvements in form of the micellar formulation together with the desirable activity consistently observed over decades of research both in terms of the nature of the drugs' biological effects as well as in highly relevant models of acute lung injury provides the rationale for the clinical trial which is to be activated per this announcement.

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ANNEXURE A

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ANNEXURE B

Name and any unique identifier of the trial:	A Phase II, double blind placebo controlled clinical trial designed to evaluate the effect of ArtemiC in patients diagnosed with COVID-19 (ID: MOH_2020-04-16_008859)
Primary endpoint(s):	• Time to clinical improvement, defined as a national Early Warning Score 2 (NEWS2) of </= 2 Maintained for 24 Hours in comparison to routine treatment • Percentage of participants with definite or probable drug related adverse events
Secondary endpoints:	• Time until negative PCR • Proportion of participants with normalization of fever and oxygen saturation through day 14 since onset of symptoms • COVID-19 related survival • Incidence and duration of mechanical ventilation • Incidence of Intensive Care Init (ICU) stay • Duration of ICU stay • Duration of time on supplemental oxygen
Blinding status:	Double Blinded
Product status:	The Product will be packaged and labelled in compliance with Good Manufacturing Practice (GMP)
Treatment method, route, frequency, dose levels:	**Agent name and composition:** ArtemiC, medical spray composed of a combination of 6 mg/ml of Artemisinin and 20 mg/ml of Curcumin. **Dose:** Maximum dose during a day by medicated spray, divided over 2 times day. **Study Procedures:** The study will last 2 weeks and additional time required for follow up till hospital discharge in order to check side effects and study drug efficacy. **Methodology:** Safety will be assessed through collection and analysis of adverse events, blood and urine laboratory assessments and vital signs. After Screening visit, the study drug will be administrated during 2 days twice a day. All patients will be monitored till the hospital discharge.
Number of trial subjects:	50 adult patients who suffer from COVID-19 infection
Description of Control Group:	Placebo + Standard of Treatment
Subject selection criteria:	**Inclusion Criteria:** • Confirmed SARS-CoV-2 infection • Hospitalized COVID-19 patient in stable moderate condition (i.e., not requiring ICU admission) • Age – 40-75 • Subjects must be under observation or admitted to a controlled facility or hospital (home quarantine is not sufficient) **Exclusion Criteria:** • Tube feeding or parenteral nutrition. • Patients who are symptomatic and require oxygen (Ordinal Scale for Clinical Improvement score >3) at the time of screening • Respiratory decompensation requiring mechanical ventilation • Uncontrolled diabetes type 2 • Autoimmune disease • Pregnant or lactating women • Admission to ICU > 24 hours • Any condition which, in the opinion of the Principal Investigator, would prevent full participation in this trial or would interfere with the evaluation of the trial endpoints.
Trial locations:	Israel – Nazareth Hospital EMMS
Name of the principal investigator:	Dr Ameer Elemy
Partners:	Galilee-CBR (CRO)
Expected duration:	The trial is expected to commence April 2020 and conclude around September 2020 with results then available in October 2020
Additional information:	Recruitment will start following placement of clinical trial insurance. Issues with recruitment are not expected however if this does occur could impact expected commencement date
Trial standard:	This clinical trial will be conducted in compliance with Good Clinical Practices (GCP)

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