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The Manager Companies
ASX Limited
20 Bridge Street
SYDNEY NSW 2000 (4 pages by email)

Dear Madam,

BIT225-012 PHASE 2 COVID-19 CLINICAL TRIAL

The Directors of Biotron Limited ('Biotron' or 'the Company') (ASX: BIT) advise the following update on the BIT225-012 Phase 2 clinical trial of its lead antiviral drug BIT225 for treatment of COVID-19.

The trial met the primary safety and tolerability end point with observed adverse events congruent in severity and frequency with those seen in previous trials of BIT225.

The trial did not meet the primary efficacy end point in this population assessed by the change in SARS-CoV-2 nasal viral load. There were no statistically significant differences between drug and placebo groups based on change in SARS-CoV-2 nasal viral load, kinetics of change or time to negative SARS-CoV-2 PCR when compared to baseline values on Day 1 to dosing completion on Day 7.

The groups were similar in terms of time to sustained clinical recovery and time to clinical improvement.

Day 1 to Day 7 was selected as the timeframe for the primary efficacy analyses, and pre-specified in the Statistical Analysis Plan (SAP). Analyses were performed as set out in the SAP, in accordance with Good Clinical Practice (GCP), and international regulatory requirements.

Once the dataset was complete, and unblinded, it was noted that four (4) trial participants did not demonstrate quantifiable levels of nasal SARS-CoV-2 virus on Day 1. All participants had positive PCR at entry (Day 1); however, in these four individuals' levels of viral RNA were below the limits of quantification. A *post hoc*, exploratory evaluation from Day 3, when all participants had quantifiable viral load measurements, to Day 9 was performed.

In this analysis nasal viral load declines slowed in the Placebo group after Day 6, while continuing at a relatively consistent rate in the two BIT225 dosage groups, resulting in lower viral loads in the BIT225 dosage groups compared to placebo. The difference between the active (BIT225) and placebo arms was significant ($P = 0.02$), especially in those starting with higher initial viral loads.

While of interest, and potentially informing further study of BIT225 in SARS-CoV-2 infection, these *post hoc* exploratory analyses do not change the formal outcomes of the trial.

In considering the results of this study the following should be noted:

1. The trial was, at the outset, restricted by Thai health and regulatory authorities to recruiting only those individuals with low to moderate risk of severe COVID-19, and under 60 years of age. The benefits of any antiviral therapy in a relatively young population with mild symptoms, and little risk of progression to severe disease is unknown.

2. A number of the drug-related adverse events seen with BIT225 in this, and previous trials, are identical to SARS-CoV-2-related symptoms, which made apportioning causality and efficacy difficult.

Michelle Miller, Biotron's Managing Director, said:

"*We remain optimistic re the potential of this new class of drugs to target significant viral infections, including SARS-CoV-2. Our preclinical data in a mouse COVID-19 model that supported the BIT225-012 clinical study remain some the best in the field (https://www.biotron.com.au/wp-content/uploads/2023/09/Plos-Pathogens-Manuscript-SARS-CoV-2.pdf).*

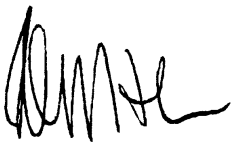
Demonstrating efficacy of new drugs to treat this disease is difficult in small trials, conducted in people without high risk of progression to severe COVID, who are excluded from investigative, placebo-controlled trials. The widespread availability of vaccination as well as immunity due to prior infection with SARS-CoV-2 contribute to challenges in demonstrating clinical efficacy in these trials.

Biotron remains focused on its platform of viroporin antagonists which uniquely combine direct-acting antiviral and immunomodulatory activities across numerous viruses responsible for important human disease.

We would like to thank the principal investigators, trial sites, CROs, and most importantly, the trial participants who enrolled in the study."

This announcement has been approved by the Company's Managing Director.

Yours sincerely



Peter J. Nightingale
Company Secretary

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ADDENDUM
SUMMARY OF BIT225-012 DESIGN

BIT225-012 (ACTRN12623000035628/ UTN U1111-1286-7528): A Phase 2, Double Blind Placebo-Controlled Study of BIT225, an Orally Administered SARS-CoV-2 Viroporin Inhibitor, to Evaluate Antiviral Activity, Safety, and Immune Biomarkers in Non-Hospitalised Vaccinated and Unvaccinated Adults with COVID-19.

The primary objectives of the study are to:

- Determine the safety and tolerability of BIT225 when dosed at 200mg or 400 mg per day, or matching placebo administered for 7 consecutive days in individuals newly diagnosed with SARS-CoV-2 within 3 days of the first onset of symptoms. Safety will be assessed by the frequency of adverse events.
- Determine the efficacy of BIT225 when dosed at 200 mg, 400 mg per day, or matching placebo administered for 7 consecutive days in individuals diagnosed with SARS-CoV-2 within 3 days of the onset of symptoms, based on SARS-CoV-2 nasal viral load, kinetics of change, and time to negative SARS-CoV-2 PCR. Efficacy endpoints will include change in SARS-CoV-2 nasal viral load, kinetics of change, and time to negative PCR.

Secondary objectives of the study are to:

- Determine the efficacy of BIT225 when dosed at 200 mg, 400 mg per day, or matching placebo administered for 7 consecutive days in individuals diagnosed with SARS-CoV-2 within 3 days of the onset of symptoms, based on multiple clinical and immunological outcome measures as follows:
    - Time to sustained clinical recovery (targeted symptom resolution)
    - Time to clinical improvement
    - Rate of hospitalisation through Day 21
    - Rate of all-cause mortality through Day 21
    - Rate of recrudescent / recurrent SARS-CoV-2 infection
- Characterise disease-specific immune and inflammatory markers, including CD8 counts, CD4/CD8 ratio, pro-inflammatory cytokines, including IL-1β, IL-6, and markers of inflammation, such as sCD163.

Study Design:

BIT225-012 is a double-blinded, placebo controlled, randomised (1:1:1), multi-site Phase 2 trial designed to evaluate BIT225 at 200mg and 400 mg daily dose versus common placebo, to be conducted at approximately three sites in Thailand. The study will enrol both SARS-CoV-2 vaccinated and unvaccinated men and women, age < 60 years. Clinical, virologic and immunologic outcomes will be analysed by baseline SARS-CoV-2 nasal RNA and vaccine status. Individuals, 18 to 59 years of age who meet all inclusion criteria and no exclusion criteria, will be enrolled.

Up to 60 individuals, up to 20 in each of the BIT225 dosage arms, and up to 20 in the common placebo arm will be enrolled.

Treatment with either BIT225, as 100 mg capsules; 200 mg or 400 mg per day or matching placebo, will begin on Day 1 and continue for 7 consecutive days, followed by a fourteen (14) day follow-up period.

Study Population:

Up to 60 adult male and female individuals from ages 18 to 59 years, diagnosed with SARS-CoV-2 within 3 days of the onset of symptoms.

About Biotron

Biotron Limited is engaged in the research, development, and commercialisation of drugs targeting significant viral diseases with unmet medical need. The Company has BIT225 in clinical development for HIV-1 and COVID-19, and additional promising preclinical programs including HBV. In addition, Biotron has several earlier stage programs designing drugs that target a class of virus protein known as viroporins which have a key role in the virus life cycle of a very broad range of viruses, many of which have caused worldwide health issues such as Coronavirus, Dengue, Ebola, Middle East Respiratory virus, Influenza and Zika viruses.

Enquiries

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