ASX Announcement

VIRALEZE Protects Against SARS-CoV-2 in Challenge Model

- **Data showing the ability of VIRALEZE™ to protect animals and reduce their level of infection (viral load) in a humanized animal model of SARS-CoV-2 infection has been published in the peer-reviewed journal, *Viruses*, in a special issue titled, *Medical Interventions for Treatment and Prevention of SARS-CoV-2 Infections*[1]**
- **VIRALEZE™ administered nasally reduced viral load by >99.9% (vs. saline control) in the lungs and trachea of animals[2] challenged with SARS-CoV-2**
- **The protective effects of VIRALEZE™ against SARS-CoV-2 in animals are consistent with the previously reported *in vitro* virucidal activity of SPL7013 (antiviral agent in VIRALEZE™, which reduces infectious SARS-CoV-2, including the Delta variant, by >99.9% within 30 seconds of exposure**
- **Viral load (amount of virus) in the nasal cavity of animals treated with VIRALEZE™ was also significantly lower (>90%) compared with the control animals**
- **Pro-inflammatory cytokines, which contribute to severe illness and death in humans with COVID-19 ("cytokine storm"), were also significantly lower in VIRALEZE™ treated animals compared with the control animals**
- **Remarkably, VIRALEZE™ treated animals had no infectious virus detected in brain or liver, in contrast to all control animals**
- **Combined findings indicate that VIRALEZE™ is highly effective in inactivating virus *in vivo*, resulting in reduced viral load exposure, reduced pro-inflammatory cytokine production, and a significant reduction in the severity of SARS-CoV-2 replication and pathogenesis**
- **VIRALEZE™ is a broad-spectrum antiviral nasal spray registered in Europe and India, and available in certain markets online. VIRALEZE™ is not approved for sale or supply in Australia**

Melbourne, Australia; 23 August 2021: Starpharma (ASX: SPL, OTCQX: SPHRY) today announced publication of new data demonstrating the protective efficacy of VIRALEZE™ antiviral nasal spray against SARS-CoV-2 challenge *in vivo* in a humanised mouse model of coronavirus infection. The results of the study have been published in the international peer-reviewed journal, *Viruses*, in a special issue titled, *Medical Interventions for Treatment and Prevention of SARS-CoV-2 Infections* (https://www.mdpi.com/1999-4915/13/8/1656).

The model used in this study of VIRALEZE™ is one of the few animal models endorsed by the World Health Organisation (WHO) to accelerate the testing of vaccines and therapeutic agents for COVID-19.[3] The transgenic mouse model expresses the human angiotensin converting enzyme (hACE2) receptor used by SARS-CoV-2 to infect cells in the human nasal cavity and respiratory tract.

The study, conducted at The Scripps Research Institute in the US, showed that VIRALEZE™ administered nasally significantly reduced viral load by more than 99.9% in the lungs and

[1] https://www.mdpi.com/1999-4915/13/8/1656
[2] The study used the K18-hACE2 mouse model, which is an *in vivo* humanised mouse model that expresses the human angiotensin converting enzyme (hACE2) receptor, the receptor used by SARS-CoV-2 to infect cells in the human nasal cavity and respiratory tract.
[3] Muñoz-Fontela, C., Dowling, W.E., Funnell, S.G.P. *et al.* Animal models for COVID-19. *Nature* **586,** 509–515 (2020). https://doi.org/10.1038/s41586-020-2787-6

trachea of animals challenged with SARS-CoV-2, compared with the virus levels in control animals. Animal challenge models of SARS-CoV-2 provide an opportunity to investigate aspects of the pathogenesis of disease that are not easily, nor able to be, studied in humans.

The impressive protective effects of VIRALEZE™ against SARS-CoV-2 in this animal model are entirely consistent with the previously reported *in vitro* virucidal activity of SPL7013[4], which has been shown to reduce infectious SARS-CoV-2, including the Delta Variant of Concern, by >99.9% within 30 seconds of exposure.

The production of pro-inflammatory cytokines ("cytokine storm"), in response to SARS-CoV-2 challenge, which can cause significant illness and death in humans after SARS-CoV-2 infection was also significantly reduced in VIRALEZE™ treated animals with compared to control animals.

VIRALEZE™ nasal spray also significantly reduced SARS-CoV-2 viral load in the nasal cavity of treated animals, and remarkably, the same animals had no infectious SARS-CoV-2 virus in both brain or liver, in contrast to all control animals, which had significant levels of virus.

Collectively, these data illustrate, in this *in vivo* animal model, the ability of nasally administered VIRALEZE™ to inactivate virus and reduce viral load in the nose, trachea, lung and blood, and the resulting protective benefits of this action on the inflammatory cytokine response.

VIRALEZE™ is a broad-spectrum antiviral nasal spray that has been developed by Starpharma with the intention of being applied in the nasal cavity to help reduce exposure to viable viral load, thereby helping to protect from infection with respiratory viruses, including SARS-CoV-2. The antiviral agent in VIRALEZE™, SPL7013, has been shown *in vitro* to have potent antiviral and virucidal activity in multiple respiratory viruses and multiple variants of SARS-CoV-2, including inactivation of >99.9% of the Delta variant, as previously announced.

The current study conducted at the Scripps Research Institute used the K18-hACE2 mouse model[5] to evaluate the anti-SARS-CoV-2 efficacy of VIRALEZE™ antiviral nasal spray. This model is an established challenge model for investigation of coronavirus SARS-CoV-2 infection, where the animals express the human ACE2 receptor that is responsible for mediating virus and cell receptor interactions (i.e., allowing virus to enter the cell, which leads to infection).

These new data provide *in vivo* validation that the nasal administration of VIRALEZE™ inactivates virus, resulting in:

- reduced viral load in the respiratory tract (nose, trachea, lungs),
- reduced virus replication in the nasal cavity and respiratory tract,
- reduced pro-inflammatory cytokine production, and
- a significant reduction in the extent and severity of SARS-CoV-2 replication and pathogenesis caused by SARS-CoV-2 infection via the nasal passages.

Data from around the world indicate that vaccines against COVID-19 are highly effective in preventing hospitalisation and death, but that vaccinated individuals can still become infected and shed virus. Complementary interventions that can reduce viral load at the primary site of initial infection will therefore continue to be helpful to reduce transmission of virus from infected

[4] Paull, J.R.A. et al. Virucidal and antiviral activity of astodrimer sodium against SARS-CoV-2 *in vitro* (2021). Antiviral Research. https://doi.org/10.1016/j.antiviral.2021.105089
[5] The Jackson Laboratory (Bar Harbor, ME, USA; Stock No. 034860)

individuals, particularly in the current environment where the dominant variants of SARS-CoV-2 (Alpha, Beta, Gamma and Delta) have higher transmission rates and have demonstrated evidence of vaccine escape.

In commenting on the significance of these findings, internationally recognised virologist, Professor Philippe Gallay, said:

"This proof-of-concept virus challenge study demonstrated that VIRALEZE™ nasal spray halts SARS-CoV-2 infection in the nose and protects the body from virus invasion of the lung, trachea, brain and liver. The reduction in nasal and tissue viral load coincides with a reduction in the production of proinflammatory cytokines and chemokine in the blood and respiratory tissues. These cytokines include IL-6, IL-1 and chemokine MCP-1 that are associated with severe COVID-19.

"These data support the hypothesis that VIRALEZE™ has the potential for personal use to help protect from the aggressive spread of respiratory virus infection, including with the globally important SARS-CoV-2 Variants of Concern, and may help to reduce the severity or frequency of respiratory, central and gastrointestinal clinical outcomes from infection."

Starpharma CEO, Dr Jackie Fairley, commented on the results:

"*It is exciting to see VIRALEZE™ demonstrate highly protective effects against SARS-CoV-2 in an established, WHO-recommended animal model of coronavirus infection. These results provide compelling data supporting the utility of a broad-spectrum nasal spray, like VIRALEZE™, to reduce exposure to virus, and reduced virus in respiratory tract and other organs, and prevention of pro-inflammatory cytokines, which are important to the pathogenesis of COVID-19.*

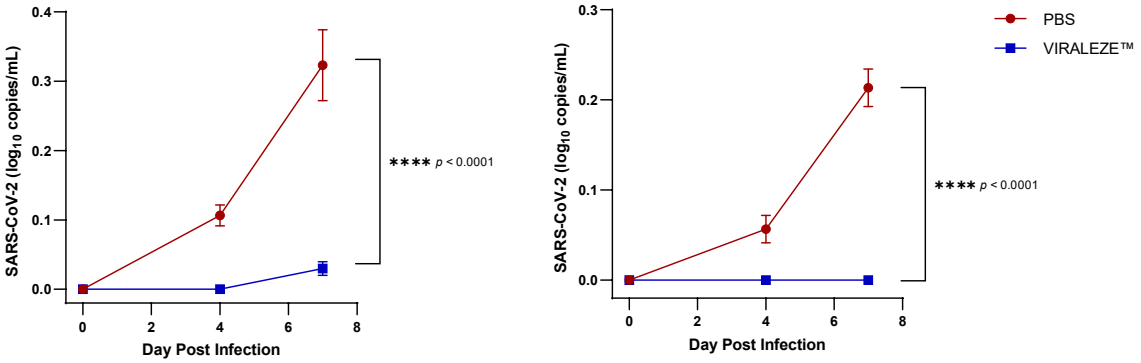
"The combination of the antiviral and virucidal activity of SPL7013 in multiple respiratory viruses and multiple variants of SARS-CoV-2, including Alpha, Beta, Gamma and Delta, with this new animal data, provides further validation for VIRALEZE™ to be potentially used as a preventative measure against respiratory viruses. One of the potential advantages of VIRALEZE™ that these data in this rigorous animal model support, is its ability to significantly reduce viral load in the respiratory tract, which would lower both the transmissibility of the virus to others and severity of disease."

Experimental Details

In this experiment, animals received VIRALEZE™ intranasally once per day for 7 days and were infected intranasally with SARS-CoV-2 (2019n-CoV/US-WA1/2020 strain) 5 minutes after the first product administration (N=3). A control group (N=3) was administered phosphate buffered saline (PBS) and infected intranasally with SARS-CoV-2 (antiviral groups). Additional groups were treated with virus that had been exposed to VIRALEZE™ (N=3) or PBS (N=3), prior to challenge (virucidal groups).

Treatment of animals with VIRALEZE™ markedly reduced SARS-CoV-2 viral load detected in blood compared with PBS, while pre-treatment of virus with SPL7013 prior to nasal infection resulted in no detectable viral load in blood (Figure 1).

Viral Load in Blood of SARS-CoV-2 infected K18-hACE2 mice treated with PBS or VIRALEZE™



(a) (b)

Figure 1. A seven-day time course of SARS-CoV-2 (USA-WA1/2020) in blood in K18-hACE2 mice (a) treated intranasally with PBS or VIRALEZE™ nasal spray and infected with SARS-CoV-2 (USA-WA1/2020) or (b) infected with SARS-CoV-2 (USA-WA1/2020) inoculum pre-incubated with PBS or VIRALEZE™ nasal spray. Viraemia was detected by qRT-PCR for SARS-CoV-2. Points and error bars represent mean ± SD. Statistical analyses were two-way analyses of variance (ANOVA) with Bonferroni multiple comparisons.

In antiviral (where VIRALEZE™ was administered before challenge) and virucidal groups (where virus is exposed to VIRALEZE™ before challenge), viral load in the nasal cavity of VIRALEZE™-treated mice was significantly reduced compared with those treated with PBS (Figure 2).

Viral Load in Nasal Cavity of SARS-CoV-2 infected K18-hACE2 mice treated with PBS or VIRALEZE™

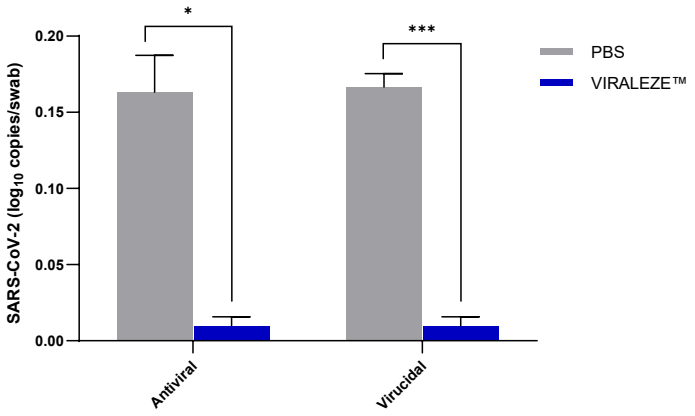


Figure 2. The number of SARS-CoV-2 (USA-WA1/2020) viral genome copies (qRT-PCR) on Day 7 per nasal swab from K18-hACE2 mice treated with PBS or VIRALEZE™ nasal spray and infected with SARS-CoV-2 (USA-WA1/2020) (Antiviral) or infected with SARS-CoV-2 (USA-WA1/2020) inoculum pre-incubated with PBS or VIRALEZE™ nasal spray (Virucidal). Columns and error bars represent mean ± SEM. * $p < 0.05$, *** $p < 0.001$, paired t-tests.

Similarly, viral load in the lung, trachea, brain and liver of VIRALEZE™-treated mice at Day 7 was significantly reduced compared with those treated with PBS. Notably, viral load in the lung and trachea were reduced by >99.9% (>3 log) in animals treated with VIRALEZE™ compared to PBS (Figure 3). Remarkably, infectious virus was reduced to zero in brain and liver of animals treated with VIRALEZE™ (refer to full publication).

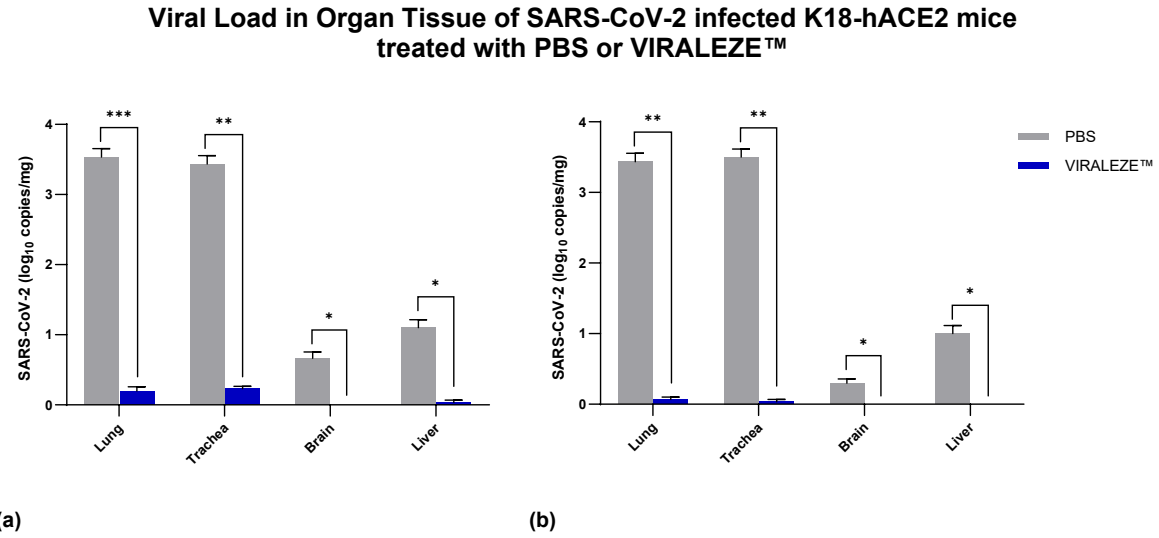


Figure 3. The number of SARS-CoV-2 (USA-WA1/2020) viral genome copies (qRT-PCR) per mg of lung, trachea, brain and liver tissue from K18-hACE2 mice (a) treated with PBS or VIRALEZE™ nasal spray and infected with SARS-CoV-2 (USA-WA1/2020) or (b) infected with SARS-CoV-2 (USA-WA1/2020) inoculum pre-incubated with PBS or VIRALEZE™ nasal spray. Tissue collected on Day 7. Columns and error bars represent mean ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, paired t-tests.

The production of several pro-inflammatory cytokines/chemokines in response to SARS-CoV-2 challenge was investigated, as the severity of COVID-19 has been related to the development of a “cytokine storm”, which is initiated and sustained by pro-inflammatory signalling that leads directly to disease progression. Pro-inflammatory cytokine/chemokine production was significantly reduced in animals treated with VIRALEZE™ compared to those treated with PBS (see Figure 4 for representative cytokine/chemokine data).

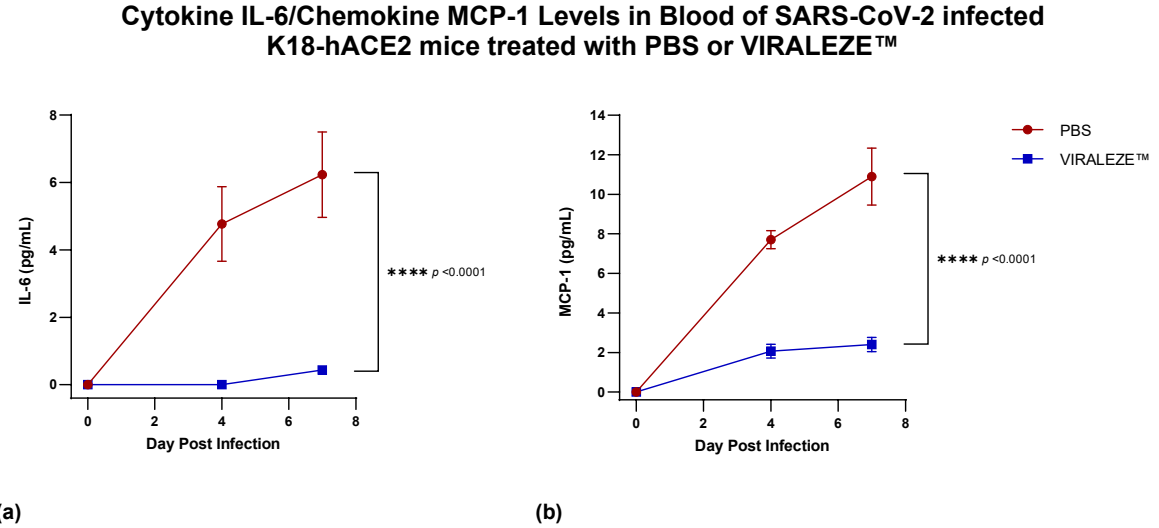


Figure 4. A seven-day time course of (a) cytokine (interleukin [IL]-6) and (b) chemokine (monocyte chemoattractant protein [MCP]-1) levels in blood in K18-hACE2 mice treated intranasally with PBS or VIRALEZE™ nasal spray and infected with SARS-CoV-2 (USA-WA1/2020). Points and error bars represent mean ± SD. Statistical analyses were two-way analyses of variance (ANOVA) with Bonferroni multiple comparisons.

Full data are available in the publication available online at https://www.mdpi.com/1999-4915/13/8/1656.

VIRALEZE™ Antiviral Nasal Spray

VIRALEZE™ contains SPL7013, which has been shown in laboratory studies to inactivate a broad spectrum of respiratory/cold viruses, including SARS-CoV-2 and variants, influenza and RSV. VIRALEZE™ is registered for sale in Europe and India. VIRALEZE™ is not registered for sale or supply in Australia.

SPL7013 is also included in products registered in >45 countries and available for sale in the UK, Europe, Japan, South East Asia, Australia and New Zealand.

Starpharma acknowledges the $1 million in funding for the development of VIRALEZE™ provided by the Australian Government's Medical Research Future Fund (MRFF) Biomedical Translation Bridge (BTB) Program, with support from UniQuest. Delivered by MTPConnect, the Australian Government's BTB program is a $22.3 million MRFF initiative that provides up to $1 million in matched funding to nurture the translation of new therapies, technologies and medical devices through to proof of concept to turn innovative medical ideas into reality.

This study was conducted in strict accordance with protocols approved by The Scripps Research Institute Ethics Committee, the Institutional Animal Care and Use Committee, and with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institute of Health (NIH). Starpharma is committed to upholding clear and strong bioethics principles and conducts its business in accordance with the highest standards of bioethics, throughout all areas of its business. These principles guide Starpharma in the conduct of clinical trials and the welfare of patients, the treatment of animals and the use of medical knowledge.

About Starpharma

Starpharma Holdings Limited (ASX:SPL, OTCQX:SPHRY) is a global biopharmaceutical company and a world leader in the development of new pharmaceutical and medical products based on proprietary polymers called dendrimers, with programs for respiratory viruses, DEP® drug delivery and VivaGel®. Starpharma has developed VIRALEZE™, an antiviral nasal spray that is registered for sale in the UK/Europe and India, and available in certain markets via www.viraleze.co. VIRALEZE™ is not approved for sale or supply in Australia. SPL7013 is utilised in approved products - the VivaGel® condom and VivaGel® BV. VivaGel® BV has been licensed in >160 countries, is approved in >45 countries and available for sale in the UK, Europe, Japan, South East Asia, South Africa, Australia and New Zealand.

As a leading company in dendrimer-based drug delivery, Starpharma's proprietary drug delivery platform technology, DEP®, is being used to improve pharmaceuticals, to reduce toxicities and enhance their performance. There are numerous internal and partnered programs underway to develop DEP® versions of existing drugs, particularly in the area of anti-cancer therapies. DEP® partnerships include oncology programs with AstraZeneca, with Merck in the area of Antibody Drug Conjugates (ADCs), with Chase Sun in the area of anti-infectives and other world leading pharmaceutical companies. Starpharma's partnered DEP® programs have the potential to generate significant future milestones and royalties.

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Disclosure
This ASX Announcement was authorised for release by the Chairman, Mr Rob Thomas.

Forward Looking Statements

This document contains certain forward-looking statements, relating to Starpharma's business, which can be identified by the use of forward-looking terminology such as "promising", "plans", "anticipated", "will", "project", "believe", "forecast", "expected", "estimated", "targeting", "aiming", "set to", "potential", "seeking to", "goal", "could provide", "intends", "is being developed", "could be", "on track", or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other authorities' requirements regarding any one or more product candidates nor can there be any assurance that such product candidates will be approved by any authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialization of the product candidates could be affected by, among other things, unexpected trial results, including additional analysis of existing data, and new data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected. Starpharma is providing this information as of the date of this document and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise. Clinical case studies and other clinical information given in this document are given for illustrative purposes only and are not necessarily a guide to product performance and no representation or warranty is made by any person as to the likelihood of achievement or reasonableness of future results. Nothing contained in this document nor any information made available to you is, or shall be relied upon as, a promise, representation, warranty or guarantee as to the past, present or the future performance of any Starpharma product.