ASX Announcement

SPL7013 nasal spray for COVID-19 – development update

- **Product development activities for SPL7013, repurposed as an antiviral nasal spray, are now well advanced with formulations developed, a manufacturer selected and pilot manufacture undertaken**
- **Additional antiviral testing of SPL7013 has been completed, confirming potent antiviral activity against SARS-CoV-2 and providing supporting data on mechanism of action indicating that SPL7013 acts early in the viral replication cycle**
- **Potent activity of SPL7013 against SARS-CoV-2 was evident when used either before or after exposure to the virus**
- **Compiled regulatory documentation in preparation for submission; an expedited regulatory pathway has been confirmed for a number of important markets including Europe**
- **A publication of the antiviral data has been submitted to peer reviewed scientific journal and is now available on bioRχiv[1]**

Melbourne, Australia; 25 August 2020: Starpharma (ASX: SPL, OTCQX: SPHRY) today announced progress with development, regulatory and manufacturing activities associated with a nasal spray for protection against COVID-19 based on the company's proprietary antiviral dendrimer, SPL7013.

Starpharma has undertaken extensive development activities for the SPL7013 nasal spray. To date, SPL7013 has been reformulated into several nasal spray formulations, the company has identified a manufacturer and device components, undertaken pilot manufacture, and compiled regulatory documentation in preparation for submission. Based on discussions with regulators, the company expects to be able to expedite approval of a SPL7013 nasal spray by leveraging existing nonclinical and clinical data of Starpharma's currently approved and marketed products.

As first announced in April, data has shown the potent antiviral activity of SPL7013 against SARS-CoV-2 (the virus that causes COVID-19). Extensive antiviral data has been generated and submitted to a peer reviewed scientific journal and is now available on the preprint server, bioRχiv.[2]

The data confirms that SPL7013 inhibits infection of host cells by SARS-CoV-2 when it is applied to the cells either before *or* after exposure to the virus (see Figure 1 below). The selectivity of SPL7013 for SARS-CoV-2 in these assays was very high (selectivity index[3] up to ~2200), indicating potent antiviral efficacy compared with minimal cellular toxicity. The selectivity index is a measure of therapeutic window. The high selectivity index of SPL7013 compares very favourably with the selectivity index against SARS-CoV-2 reported in the literature of 279 for remdesivir and 172 for chloroquine.[4]

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[1] bioRχiv (pronounced "bio-archive") is a preprint website for biology to allow early access to scientific manuscripts operated by Cold Spring Harbor Laboratory in the US. https://doi.org/10.1101/2020.08.20.260190

[2] Paull, J.R.A. et al., 2020. Astodrimer sodium, dendrimer antiviral, inhibits replication of SARS-CoV-2 *in vitro*. bioRχiv 2020.08.20.260190. https://doi.org/10.1101/2020.08.20.260190

[3] Selectivity index is a ratio of antiviral activity to cellular toxicity. The higher the selectivity index, the theoretically safer and more effective a compound would be in humans.

[4] Pizzorno, A., et al., 2020. *In vitro* evaluation of antiviral activity of single and combined repurposable drugs against SARS-CoV-2. *Antiviral Res.* 104878. Advance online publication. https://doi.org/10.1016/j.antiviral.2020.104878

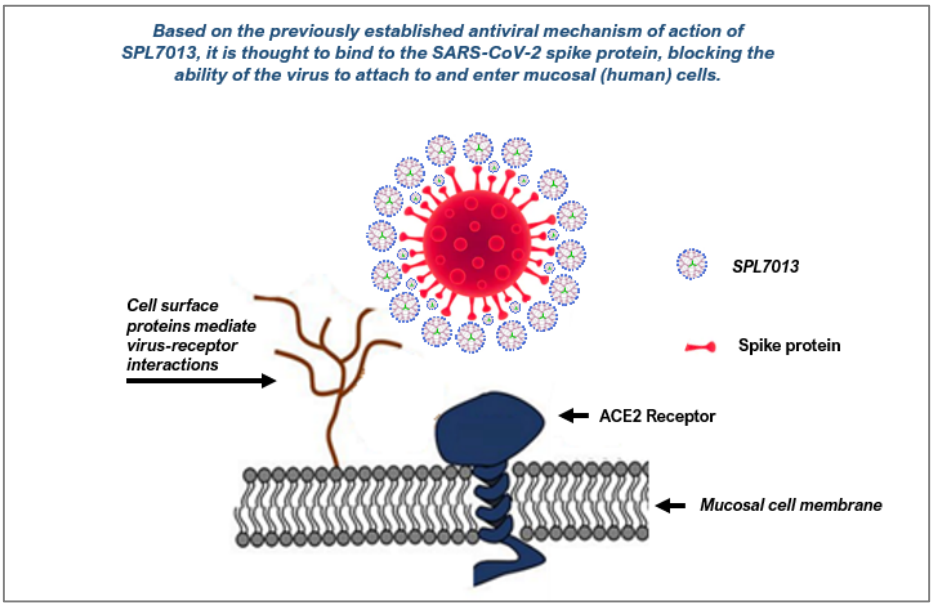
In an assay to detect virucidal activity, SPL7013 also rendered SARS-CoV-2 inactive and prevented infection when it was mixed with the virus prior to adding to cells.

The high potency and high selectivity index of SPL7013 indicate that a final formulated product can and will have a concentration of SPL7013 that is several thousand-fold higher than the concentration shown to exert an antiviral effect on SARS-CoV-2.

SPL7013 has broad spectrum antiviral and virucidal effects, with activity demonstrated against a range of viruses, including HIV, herpes simplex virus (HSV), human papillomavirus (HPV), adenovirus, H1N1 influenza virus, hepatitis B virus (HBV) and Zika virus. Given the broad antiviral activity, a SPL7013 nasal spray also has potential for application beyond SARS-CoV-2 for other common respiratory viruses, and could be useful in pandemic preparedness in the future.

Mechanism of action

SPL7013 inactivates viruses by blocking the interaction between viral surface proteins and the human cell receptor proteins. As for other viruses inhibited by SPL7013, SARS-CoV-2 infects human cells by using the characteristic viral surface proteins, or “spikes”, to attach to receptor proteins on the surface of human cells.



The data generated indicate that SPL7013 acts early in the SARS-CoV-2 replication cycle. When SPL7013 was added to cells before or at various stages of the virus replication lifecycle after infection with SARS-CoV-2, no infectious virus was detected, regardless of the initial time of addition of SPL7013 (see Figure 2 below). This finding was in contrast to other antivirals, remdesivir and hydroxychloroquine, for which infectious *virus was detectable at all times of addition*, when tested in the same assay. Remdesivir only partly reduced infectious virus when it was added at early stages of the virus replication lifecycle, while hydroxychloroquine did not reduce infectious virus at any time of addition.

These data are consistent with SPL7013 inhibiting the initial stages of SARS-CoV-2 attachment and entry into cells, and inactivating the virus, as has been demonstrated for other viruses such as HIV. This mechanism of action, the high selectivity described above, and the fact that it is a large dendrimer molecule that is not systemically absorbed, make SPL7013 well-suited to being applied topically as a nasal spray to help prevent SARS-CoV-2 infection.

SPL7013 is the active ingredient in marketed VivaGel® products and has been shown to be safe and well tolerated in multiple large international clinical trials. VivaGel® products are approved and marketed in the UK, Europe, Asia, Canada, Australia, and New Zealand, and are already manufactured at industrial scale.

SPL7013 active is already scaled up for commercial supply, and the availability of existing stocks of SPL7013 will further expedite development and commercialisation of the nasal spray product.

Dr Jackie Fairley, Starpharma CEO, commented: "We are pleased to provide an update on the progress with development of the SPL7013 nasal spray. The potent activity of SPL7013 in SARS-CoV-2, its action early in the replication cycle and its selectivity are all positive product features. Whilst effective vaccines will be central to the fight against COVID-19, other preventative measures will continue to be important to reduce the risk of transmission and exposure to SARS-CoV-2. Our strategy for the product includes leveraging Starpharma's vast body of existing technical data and existing regulatory approvals for SPL7013, to fast-track the regulatory and commercialisation pathways to have the product ready for market as soon as possible."

The SPL7013 nasal spray has the potential to complement vaccine strategies to further reduce risk by preventing acquisition and transmission of SARS-CoV-2, and reducing disease progression due to ongoing viral replication in mild forms of COVID-19. Feedback from infectious disease specialists and other healthcare agencies has confirmed that a cost-effective and readily available product to help prevent SARS-CoV-2 infection would be highly valued and play an important role in reducing transmission for the broader population and especially for frontline workers in the health, aged care and travel industries.

Whilst the initial focus is on a nasal spray as the most rapid path to market, the company also notes that SPL7013 could be applied via other routes of administration, such as ocular, nebulised or injection.

The SPL7013 active is patented by Starpharma in major markets, and a specific patent application has been filed for the COVID-19 nasal spray. Starpharma has also commenced confidential commercialisation discussions, having shared product details and supporting technical data with a number of interested pharmaceutical companies, covering a range of geographic markets.

Appendix 1 – Data summary: Antiviral activity of SPL7013 against SARS-CoV-2

Figure 1 – Antiviral Efficacy Assays: Dose-response curves for the anti-SARS-CoV-2 efficacy at increasing concentrations of SPL7013 (when added prior to or post infection), as measured by reduction in SARS-CoV-2-induced cytopathic effect (CPE) in Vero E6 cells.

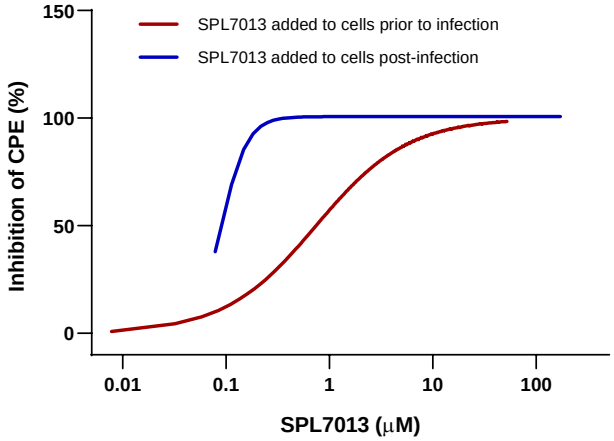
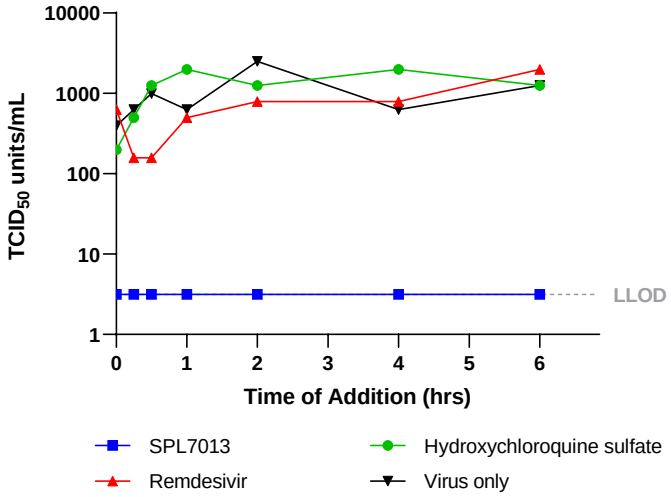


Figure 2 – Time of Addition Assay: SPL7013, remdesivir, and hydroxychloroquine sulfate were assessed for antiviral activity at early, middle and late stages of SARS-CoV-2 replication by adding compounds at different times post-infection and compared with virus only as control. Each point on the graph represents the $TCID_{50}$ (tissue culture infectious dose) of virus, which is the amount of *infectious* virus, present after one cycle of replication (8 hours post-infection) following addition of compound, at the indicated time following virus infection. For SPL7013, infectious virus was not detected at or below the lower limit of detection (LLOD) regardless of time of addition of SPL7013.

This finding was in contrast to other antivirals, remdesivir and hydroxychloroquine, for which infectious virus was detectable at all times of addition, tested in the same assay. Remdesivir only partly reduced infectious virus when it was added at early stages of the virus replication lifecycle, while hydroxychloroquine did not reduce infectious virus at any time of addition.



Testing was conducted at 360biolabs (www.360biolabs.com), an ISO-accredited commercial laboratory that offers specialised clinical virology testing, and which has access to specialist Physical Containment (PC) 3 biological facilities. Starpharma thanks Melbourne Health, the Doherty Institute and VIDRL (Victorian Infectious Diseases Reference Laboratory) for providing SARS-CoV-2 (hCoV-19/Australia/VIC01/2020) to 360biolabs to facilitate testing.

About Starpharma

Starpharma Holdings Limited (ASX: SPL, OTCQX:SPHRY), located in Melbourne Australia, is an ASX 300 company and is a world leader in the development of dendrimer products for pharmaceutical, life science and other applications.

Starpharma's underlying technology is built around dendrimers – a type of synthetic nanoscale polymer that is highly regular in size and structure and well suited to pharmaceutical and medical uses. Starpharma has two core development programs: VivaGel® portfolio and DEP® drug delivery with the Company developing several products internally and others via commercial partnerships.

VivaGel®: Starpharma's women's health product - VivaGel® BV is based on SPL7013, astodrimer sodium, a proprietary dendrimer. VivaGel® BV for bacterial vaginosis (BV), is available for sale under the brand names Betafem® BV Gel (UK), Betadine BV™ (Europe), Betadine™ BV Gel (Asia) and Fleurstat BVgel (Australia and New Zealand) and a new drug application has been submitted to the US FDA. Starpharma has licensed the sales and marketing of VivaGel® BV to ITF Pharma for the US; Mundipharma for Europe, Russia, CIS, Asia, the Middle East, Africa and Latin America; and to Aspen Pharmacare for Australia and New Zealand. Starpharma also has licence agreements to market the VivaGel® condom (an antiviral condom which includes VivaGel® in the lubricant) in several regions, including Australia, Europe, Canada, China and Japan (Okamoto). The VivaGel® condom has been launched in Japan under Okamoto's 003 brand, and in Australia and Canada under the LifeStyles Dual Protect® brand. The VivaGel® condom is approved in Europe.

DEP® - Dendrimer Enhanced Product®: Starpharma's DEP® drug delivery platform has demonstrated reproducible preclinical benefits across multiple internal and partnered DEP® programs, including improved efficacy, safety and survival. Starpharma has three internal DEP® products – DEP® docetaxel, DEP® cabazitaxel and DEP® irinotecan - in clinical development in patients with solid tumours. Starpharma's partnered DEP® programs include a multiproduct DEP® licence with AstraZeneca, which involves the development and commercialisation of two novel oncology compounds, with potential to add more. In June 2019 Starpharma signed a Development and Option agreement with AstraZeneca for a DEP® version of one of AstraZeneca's major marketed oncology medicines.

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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.