ASX Announcement

Positive DEP® phase 2 interim results in prostate cancer

- **Starpharma reports positive interim results for the prostate cancer cohort in its phase 2 DEP® cabazitaxel clinical trial, all of whom have hormone refractory, Stage IV metastatic disease**
- **One or more encouraging efficacy signals were observed in 100% of patients assessed following DEP® cabazitaxel treatment. Responses included:**
    - **64% of patients with assessable tumour lesions saw prolonged stable disease and significant reductions in tumour size for up to 36 weeks with some patients still receiving treatment**
    - **90% of patients with assessable PSA (Prostate Specific Antigen) tumour biomarker levels had a reduction in PSA, with more than half of these patients achieving a reduction in PSA of at least 50%**
    - **83% of patients with secondary bone disease exhibited either no progression or an improvement in these lesions**
    - **56% of patients who were evaluable for all three efficacy measures (above) had responses to all three**
- **Patients treated with DEP® cabazitaxel experienced significantly fewer and less-severe side effects than typically seen with conventional marketed cabazitaxel (Jevtana®), including a marked reduction in severe bone marrow toxicity (myelosuppression) which can be problematic, especially in older or patients with poorer health**
- **These positive interim results are particularly significant given all patients in this cohort had late-stage prostate cancer, and had failed multiple therapies (which included taxanes) prior to entering the DEP® cabazitaxel trial**
- **Prostate cancer is the 2nd most common cancer in males globally with 1.4 million[1] new prostate cancer patients diagnosed annually (worldwide). Sales of Jevtana® (conventional cabazitaxel) exceeded US$600 million in 2020[2] (up 12% from 2019)**

Melbourne, Australia; 25 November 2021: Starpharma (ASX: SPL, OTCQX: SPHRY) today announced positive interim results from its ongoing phase 2 trial of DEP® cabazitaxel, showing that 100% (22/22) of evaluable[3] patients with hormone refractory, (Stage IV) metastatic prostate cancer. All of these patients have been heavily pre-treated and have had efficacy responses, utilising one or more standard measures of disease.

These interim results in prostate cancer show that one or more encouraging efficacy signals were observed in 100% of patients assessed following DEP® cabazitaxel treatment, and 56% of patients who were evaluable for all three efficacy measures had responses to all three measures noted below. Responses included:

- 64% of patients with assessable tumour lesions saw prolonged stable disease and significant reductions in tumour size for up to 36 weeks with some patients still receiving treatment

[1] https://www.uicc.org/news/globocan-2020-new-global-cancer-data
[2] https://www.sanofi.com/en/investors/financial-results-and-events/financial-results/Q4-results-2020
[3] Evaluable patients are those who received ≥1 dose DEP® cabazitaxel and had an applicable efficacy assessment conducted post treatment. Total of 25 prostate cancer patients enrolled with three patients non-evaluable for efficacy outcomes but are included in safety outcomes.

- 90% of patients with assessable PSA (Prostate Specific Antigen) tumour biomarker levels had a reduction in PSA, with more than half of these patients achieving a reduction in PSA of at least 50%
- 83% of patients with secondary bone disease exhibited either no progression or an improvement in these lesions

These efficacy results are very encouraging, especially given that the prostate cancer patients enrolled in the study were very heavily pre-treated, each having received an average of four prior cancer treatment regimens and an average of more than 70 cycles/months of prior anti-cancer treatment, in addition to surgeries and radiotherapy. Many had also already received marketed taxane chemotherapies, including up to 14 cycles of Taxotere® (docetaxel) and 10 cycles of Jevtana® (conventional cabazitaxel). One patient had 10 prior treatment regimens, and almost half of the patients had received more than 90 cycles/months of therapy prior to DEP® cabazitaxel treatment.

Professor Anthony Joshua, Study Investigator from the Kinghorn Cancer Centre in Sydney with a focus in prostate cancer commented:

"The trial results to date for DEP® cabazitaxel in heavily pre-treated prostate cancer patients are highly encouraging and indicate the potential of the product compared to standard cabazitaxel. The anti-cancer activity, together with less myelosuppression than standard cabazitaxel and a generally well-tolerated safety profile, mean this novel form of dendrimer-enhanced cabazitaxel represents a useful option for prostate cancer patients, including in older patients in whom DEP® cabazitaxel has been particularly well tolerated."

Efficacy in the prostate cancer cohort in the trial was assessed referencing the applicable aspects of the internationally recognised *Prostate Cancer Working Group* (PCWG3)[4] guidelines. These guidelines recommend assessing multiple measures of disease control separately, including stable or reduced tumour lesion size, reduced levels of PSA, and/or lack of secondary bone disease progression.[5] Other applicable efficacy measures, such as time to progression (TTP), will be analysed when the ongoing prostate cancer patients have completed treatment in the study.

Patients treated with DEP® cabazitaxel also experienced significantly less severe bone marrow toxicity (myelosuppression), significantly lower rates of severe neutropenia and no instances of neutropenic sepsis, which are all significant risks associated with conventional cabazitaxel (Jevtana®). Further, the absence of detergent-like polysorbate 80[6] in the DEP® cabazitaxel formulation eliminated the need for prophylactic corticosteroids and antihistamines, with no anaphylaxis or severe hypersensitivity reactions observed.

Commenting on the results, Starpharma CEO, Dr Jackie Fairley, said,

"These positive results for DEP® cabazitaxel in Stage IV prostate cancer patients are really exciting news for Starpharma and our DEP® platform. They include high rates of efficacy across three measures of disease - tumour size, PSA, and bone metastases, and compare favourably with published data for conventional cabazitaxel, e.g., Jevtana®, particularly given the heavily pre-treated status of the patients in this trial and their older average age. These highly encouraging results include responses in patients who had previously received taxanes."

[4] Scher, H.I., et al., Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*, 2016, 34(12):1402-18.
[5] A number of the prostate cancer and other patients remain on study and other efficacy measures will be calculated once all patients finish treatment and the trial is completed.
[6] Polysorbate 80 is a detergent-like substance, which is used to solubilise insoluble molecules, and which is a component of conventional cabazitaxel products, including Jevtana® and generic forms

Data from this cohort of prostate cancer patients is being presented in confidential commercial discussions with several potential pharmaceutical companies / partners.

A total of 51 patients have now been recruited across all cancer types in the phase 2 DEP® cabazitaxel trial. These results reported today relate only to the prostate cancer patients. Recruitment of a small number of additional patients with other tumour types including heavily pre-treated ovarian and gastro-oesophageal cancer patients continues following promising efficacy signals in these tumours. Full results for the trial will be reported separately in the coming months.

The phase 2 DEP® cabazitaxel trial is being conducted at multiple sites, including Guy's Hospital in London, University College London, the Velindre Cancer Centre in Cardiff, Imperial College London, and the Kinghorn Cancer Centre in Sydney.

Interim results for the prostate cancer cohort in the phase 2 DEP® cabazitaxel trial

Of the 25 enrolled patients with prostate cancer, 22 were evaluable[7]. All patients enrolled had advanced metastatic (Stage IV) castrate-resistant/hormone refractory prostate cancer. Of these, 14 had soft tissue (non-bone) tumours, 21 had elevated and increasing levels of PSA, and 18 patients had secondary tumours in their bones, or "bone disease".

Of the patients with soft tissue prostate tumours, 64.3% (9/14) achieved prolonged disease control (stable or reduced tumour lesion size) for periods, to date, of up to 36 weeks, following treatment with DEP® cabazitaxel. Despite the heavily pre-treated status of the patients in the study, and the advanced stage of their disease, DEP® cabazitaxel achieved partial responses"[8] of up to 45% tumour size reduction compared with baseline, in 18.2% (2/11) of patients with measurable disease. This compares favourably with the published clinical study evaluating conventional cabazitaxel (Jevtana®) at the same dose (20 mg/m^2) where 18.5% of patients dosed with the equivalent amount of cabazitaxel achieved a partial response.[9]

A total of 90.5% (19/21) of patients who had elevated PSA and received DEP® cabazitaxel had a reduction in their PSA level, and 52.4% of these patients (11/21) have had a reduction of greater than 50% from baseline to date (noting some patients are still continuing treatment). This result compares very favourably with clinical studies of Jevtana® at the same dose as DEP® cabazitaxel, in which PSA reduction of >50% occurred in only 29.5% of patients.[9]

Of the patients with bone disease (secondary tumour in their bones), 83.3% (15/18) exhibited either no progression or an improvement in these lesions after commencing treatment with DEP® cabazitaxel.

Nine patients were evaluable for all three efficacy measures and 56% achieved efficacy signals in all three measures.

These very encouraging efficacy findings across multiple measures (tumour size, PSA and bone progression) are particularly impressive given patients in the trial were very heavily pre-treated with multiple prior cancer therapies and had few treatment options. Their disease had progressed on other treatments prior to enrolment in this study. Prostate cancer patients in the study had each received numerous prior treatment cycles with an average of 4 cancer treatment regimens. Prior anti-cancer therapies for the DEP® cabazitaxel patients included chemotherapy, immuno-oncology agents, hormonal therapies, radiopharmaceuticals, and targeted therapies, in addition to prior surgeries and radiotherapy.

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[7] Evaluable patients are those who received ≥1 dose DEP® cabazitaxel and had an applicable efficacy assessment conducted post treatment. Total of 25 prostate cancer patients enrolled with three patients non-evaluable for efficacy outcomes but are included in safety outcomes.

[8] Eisenhauer, E.A., et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, 2009, 45(2):228-47.

[9] Eisenberger, M., et al., Phase III study comparing a reduced dose of cabazitaxel (20 mg/m^2) and the currently approved dose (25 mg/m^2) in post docetaxel patients with metastatic castration-resistant prostate cancer—PROSELICA. *J Clin Oncol,* 2017, 35(28):3198-206.

All but one of the prostate cancer patients treated with DEP® cabazitaxel had been previously treated with marketed taxane chemotherapies, including up to 14 cycles of Taxotere® (docetaxel) and 10 cycles of Jevtana® (cabazitaxel). Compared with published data for Jevtana®, prostate cancer patients treated with DEP® cabazitaxel were approximately 6 times more likely to have received 3 or more cycles of chemotherapy prior to study entry, and more than 3 times more likely to have received 2 or more cycles. Typically, heavy pre-treatment is associated with a lower treatment response rate.

Unlike Jevtana® treated prostate cancer patients, DEP® cabazitaxel did not require daily treatment with oral corticosteroids. This avoidance of long-term steroid use is attractive, particularly in prostate cancer patients where bone health can be a significant issue.

Five of the prostate cancer patients remain on treatment in the study with no further enrolment of prostate cancer patients planned. Enrolment continues in other specific tumour types, including ovarian and gastro-oesophageal cancers, where encouraging efficacy signals have also been observed. A number of other patients in the trial with these cancers have achieved significant and sustained reductions in their tumour size (30-53% decrease).

In the trial, treatment with DEP® cabazitaxel at 20 mg/m^2 cabazitaxel has been well tolerated, and the cohort of prostate cancer patients has received up to 11 cycles. Unlike the marketed form of cabazitaxel, DEP® cabazitaxel does not require pre-treatment with antihistamines and steroids to seek to avoid life-threatening allergic and anaphylactic reactions.

The phase 2 prostate cancer patients treated with DEP® cabazitaxel have experienced significantly less bone marrow toxicity, particularly neutropenia, than is reported for Jevtana®, despite being on average approximately 5 years older (73 years of age) than those in Jevtana® registration clinical trials (average age of 68 years).[10]

In contrast to Jevtana®, treatment with DEP® cabazitaxel was associated with a notable lack of febrile neutropenia and neutropenic infections (0% DEP® cabazitaxel vs 2 - 6% with Jevtana®) and grade 3 (severe) or higher neutropenia (16% DEP® cabazitaxel vs between 42 - 82% with Jevtana®). Febrile neutropenia and neutropenic infections are both life-threatening conditions and are particularly problematic in elderly patients.

Jevtana®'s recommendation for many patients >65 years old is to receive prophylaxis with G-CSF (granulocyte colony-stimulating factor) from the first cycle (primary prophylaxis) to prevent severe/life-threatening neutropenia. Despite the higher mean age of DEP® cabazitaxel treated prostate cancer patients in this study, there has been no need to give any patients, primary G-CSF prophylaxis, including patients over 65. Furthermore, only two patients in the prostate cancer cohort have required any G-CSF therapy following an event of neutropenia.

In this cohort, DEP® cabazitaxel was generally well tolerated with the vast majority of adverse events (AEs) reported were mostly mild (grade 1)/moderate (grade 2). AEs observed with DEP® cabazitaxel are all reported with conventional cabazitaxel (Jevtana®) treatment. These included fatigue, diarrhoea, nausea, vomiting, constipation, peripheral neuropathy, decreased appetite and decreased weight. Additionally, no cases of anaphylaxis, severe hypersensitivity and hair-loss, all of which occur for Jevtana®, were observed with DEP® cabazitaxel treatment. Patients treated with conventional cabazitaxel (Jevtana®) are routinely pre-treated with corticosteroids and antihistamines to reduce the risk of life-threatening anaphylactic reactions to the excipients (detergents) present in conventional cabazitaxel. Starpharma's DEP® cabazitaxel is water soluble, eliminating the need for steroid and antihistamine pre-treatment and the absence of polysorbate-80 reduces the risk of anaphylactic reactions.

[10] Jevtana Prescribing Information https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=pi&q=Jevtana

About DEP® cabazitaxel

DEP® cabazitaxel is a patented, detergent free, nanoparticle version of the cancer drug, Jevtana®, and is currently in phase 2. Jevtana® is a leading oncology agent used to treat advanced prostate cancer with sales of more than US$600 million in 2020[2]. The current (non-dendrimer) formulation of the product has US Food and Drug Administration (FDA)-mandated 'black box' warnings in relation to neutropenia, which is a major dose limiting side effect, and severe hypersensitivity (e.g. anaphylaxis) resulting from the polysorbate-80 detergent excipient used in its formulation.

DEP® cabazitaxel is one of Starpharma's three clinical stage DEP® assets being developed internally, alongside DEP® docetaxel and DEP® irinotecan. Starpharma's intention is to licence internal DEP® assets following clinical proof-of-concept/phase-2. Starpharma also has a number of partnered DEP® programs including with Merck & Co., Inc., and also a multiproduct DEP® licence with AstraZeneca, which includes the development and commercialisation of AZD0466, a novel Bcl2/xL inhibitor, which is in the clinic.

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 online. 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 registered 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.