ASX Announcement

Positive DEP® docetaxel Phase 2 results

- Starpharma's DEP® docetaxel Phase 2 clinical trial program has yielded positive results and met its objectives, demonstrating encouraging anti-tumour activity in multiple advanced, metastatic cancers, including pancreatic, lung and gastro-oesophageal.
- DEP® docetaxel, either as monotherapy or in combination with other anti-cancer agents (nintedanib or gemcitabine), exhibited encouraging signs of efficacy in heavily pre-treated patients with advanced, metastatic cancers, including pancreatic and non-small cell lung cancer (NSCLC), as well as in patients with advanced gastro-oesophageal cancers.
- The DEP® docetaxel Phase 2 clinical trial program also confirmed the product's improved tolerability profile versus conventional docetaxel in terms of key and sometimes dose-limiting adverse events, including severe neutropenia, oedema (fluid retention), alopecia (hair loss) and allergic reactions (anaphylaxis). Some of these adverse events (severe neutropenia and anaphylaxis) can be fatal and are FDA "Black Box" warnings.
- DEP® docetaxel effectively targets tumours, as evidenced by patient biopsies after treatment, with up to 60 times higher levels of docetaxel in tumour tissue compared to blood levels.

Melbourne, Australia; 19 December 2023: Starpharma (ASX: SPL, OTCQX: SPHRY) today announces positive final results from the completed Phase 2 clinical program of DEP® docetaxel. The clinical program included a monotherapy arm and two combination arms. The Phase 2 trial objectives were met, with endpoints demonstrating encouraging anti-tumour activity of DEP® docetaxel when administered as a monotherapy or in combination with other anti-cancer agents, nintedanib or gemcitabine, in multiple advanced, metastatic cancers, including pancreatic, gastro-oesophageal, non-small cell lung cancer (NSCLC) and cholangiocarcinoma.

The safety and tolerability of DEP® docetaxel were also confirmed, with DEP® docetaxel demonstrating an improved tolerability profile versus conventional docetaxel in terms of key adverse events, including myelosuppression (severe neutropenia), oedema (fluid retention), alopecia (hair loss) and allergic reactions (anaphylaxis/hypersensitivity).

Developed by Starpharma, DEP® docetaxel is a patented, dendrimer nanoparticle version of the chemotherapy drug docetaxel (Taxotere®[1]), which achieved peak sales of US$3.1B before patent expiry and is widely used for the treatment of a number of common cancers, including lung, gastro-oesophageal, head and neck, breast, and prostate.

The clinical trial also demonstrated the ability of DEP® docetaxel to effectively target tumours, with treated patient biopsies showing that tumour tissue achieved tissue levels of docetaxel up to 60 times higher than levels in blood (Figure 1). This tumour targeting effect was demonstrated across multiple cancer types. These findings confirm the ability of DEP® to increase the delivery of drug to tumours, as also demonstrated in multiple preclinical models.

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

"We are pleased to announce positive results of the Phase 2 clinical program for DEP® docetaxel. This product has shown encouraging results in multiple difficult-to-treat cancers, both as a monotherapy and in combination with gemcitabine or nintedanib. DEP® docetaxel also demonstrated lower rates of key adverse events, including severe neutropenia, hypersensitivity, fluid retention and hair loss, all of which are problematic side effects for patients treated with conventional docetaxel. In the trial, DEP® docetaxel achieved clinically meaningful disease control in multiple patients with advanced metastatic cancer who had no other treatment options available.

"These clinical findings, in addition to Starpharma's recently reported results from the DEP® cabazitaxel and DEP® irinotecan programs, will feed into Starpharma's ongoing commercial

[1] Taxotere Label, Sanofi-Aventis, USA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020449s086lbl.pdf.

discussions for the products. These discussions will continue at the upcoming JP Morgan Healthcare Conference in San Francisco in January 2024, in which Starpharma will participate.

"Starpharma would like to thank the patients who participated in the DEP® docetaxel clinical trial program, as well as their families, caregivers, and the investigators and other clinical staff for their involvement in the program."

DEP® Docetaxel Efficacy Results

The Phase 2 clinical trial program enrolled a total of 80 patients with advanced metastatic cancers who were heavily pre-treated with up to 9 prior lines of therapy (median 3) and up to 37 cycles of prior anti-cancer treatments (median 5), and/or had exhausted all available treatment options.

DEP® docetaxel achieved encouraging anti-tumour activity in multiple advanced, metastatic cancers, including pancreatic, gastro-oesophageal, NSCLC and cholangiocarcinoma, despite the advanced nature of most patients' disease.

A number of these tumours, particularly pancreatic and gastro-oesophageal cancers, represent significant unmet medical needs, and have a very poor prognosis and limited available treatments currently. All patients in the DEP® docetaxel trial program had failed to respond to or progressed following prior cancer treatment, including taxanes, platinum-based therapy, or immuno-oncology agents.

In patients with **advanced gastro-oesophageal cancer**, DEP® docetaxel monotherapy achieved a disease control rate[2] (DCR) of 28.6% with disease control for up to 28 weeks in evaluable[3] patients.

In advanced, **metastatic non-small cell lung cancer (NSCLC)** patients, DEP® docetaxel administered in combination with nintedanib (Vargatef®) achieved a DCR of 80.0%, with disease control for up to 24 weeks.

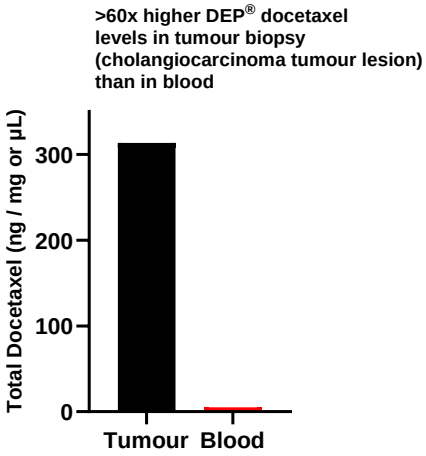
DEP® docetaxel administered in combination with gemcitabine (Gemzar®) in **advanced pancreatic cancer** patients demonstrated a 75.0% disease control rate (DCR) with disease control for up to 23 weeks. These patients had failed standard-of-care therapy and exhausted all available treatment options prior to enrolment into the trial. DEP® docetaxel, administered as monotherapy to advanced pancreatic cancer patients, exhibited a disease control rate (DCR) of 33.3% and reductions in tumour lesions of up to 55.6%.

DEP® docetaxel in combination with gemcitabine also demonstrated disease control in other difficult-to-treat advanced cancers, including intrahepatic cholangiocarcinoma and uterine sarcoma, with durable responses for up to 30 weeks. DEP® docetaxel monotherapy treatment also achieved encouraging efficacy responses in other rare and difficult-to-treat advanced cancers, including melanoma of the eye and ameloblastoma, with disease control for up to 46 weeks.

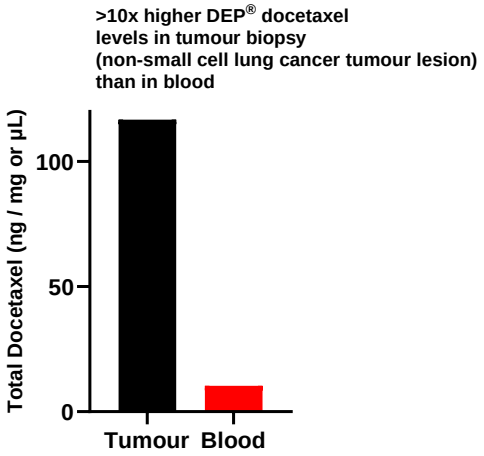
The clinical trial also demonstrated the ability of DEP® docetaxel to effectively target human tumours, with treated patient biopsies showing that tumour tissue achieved tissue levels of docetaxel that were up to 60 times higher compared to blood (Figure 1). This tumour targeting effect was demonstrated across multiple cancer types.

[2] DCR = stable disease (SD) + partial response (PR).
[3] All efficacy response data reported in this announcement are for evaluable patients. Evaluable patients are those that received ≥1 dose cycle of DEP® docetaxel and had a CT scan to assess response to treatment at ≥7 weeks after commencement of treatment with DEP® docetaxel.

Figure 1. Tumour targeting observed in patient biopsies following treatment with DEP® docetaxel, with DEP® delivering substantially higher levels of drug (docetaxel) to the tumour (10-60x) versus blood



A: Cholangiocarcinoma patient biopsy (cycle 1, day 4 post-treatment)



B: Non-small cell lung cancer patient biopsy (cycle 1, day 4 post-treatment)

DEP® Docetaxel Safety and Tolerability

DEP® docetaxel also achieved a favourable safety and tolerability profile compared with conventional docetaxel with respect to a number of that product's "Black Box" safety warnings regarding serious, life-threatening adverse events and other dose-limiting adverse events.

DEP® docetaxel exhibited reduced rates compared with conventional docetaxel for several such "Black Box" adverse events, including neutropenia and febrile neutropenia, hypersensitivity and peripheral oedema (fluid retention), as well as problematic adverse events, including mucositis (mouth ulceration), nail disorders and hair loss (alopecia) (see Table 1).

Table 1. Comparative key treatment-related adverse events (% of patients) for DEP® docetaxel monotherapy vs published data on conventional docetaxel (Taxotere®) monotherapy

Treatment-related Adverse Event	DEP® Docetaxel	Taxotere®[1]	DEP® Docetaxel	Taxotere®[1]
	Grade 3/4		All Grades	
Neutropenia	0%	75%	2%	95%
Anaemia	4%	0%	8%	65%
Hypersensitivity	0%	3%	0%	1-6%^
Hair Loss (Alopecia)	Not applicable	Not applicable	0%	>50%† (up to 10% permanent hair loss[4])

DEP® docetaxel dose: 45/60 mg/m^2 docetaxel, N=50; note: DEP® docetaxel has different pharmacokinetics compared to conventional docetaxel, so doses are not directly comparable; Conventional docetaxel (Taxotere®) dose: 60 mg/m^2 docetaxel, N=174; Not applicable: Grade 3/4 not applicable for hair loss (alopecia); ^ data for 60/75 mg/m^2 docetaxel; † data for 75 mg/m^2 docetaxel

[4] Martín M, et al. *Breast Cancer Res Treat*. 2018 Oct;171(3):627-634. doi: 10.1007/s10549-018-4855-2.

DEP® docetaxel, when administered as monotherapy or in combination with nintedanib or gemcitabine, demonstrated a marked reduction in bone marrow toxicity (myelosuppression), including fewer reports of severe (≥ grade 3) neutropenia (0% for DEP® docetaxel monotherapy and 2.5% of DEP® docetaxel patients overall) and no cases of febrile neutropenia. This contrasts with conventional docetaxel, where virtually all patients experience neutropenia, and 75 to 85% experience severe (grade 4) neutropenia[1].

Lower rates of myelosuppression in DEP® docetaxel-treated patients also resulted in fewer instances of anaemia compared to conventional docetaxel. Conventional docetaxel (60 mg/m^2) results in anaemia in more than 65% of patients, whereas only 8.0% of patients receiving DEP® docetaxel monotherapy and 10% of patients overall experienced anaemia (all grades)[1]. DEP® docetaxel-treated patients (monotherapy) experienced ≥ grade 3 anaemia at a rate of only 4.0%.

The conventional docetaxel formulation (e.g., Taxotere®) contains toxic excipients, including detergent-like polysorbate-80 and ethanol, which are associated with severe hypersensitivity reactions, including sometimes fatal anaphylaxis. To reduce the risk of these reactions, patients receiving conventional docetaxel must undergo corticosteroid (cortisone) pre-treatment. Despite this steroid pre-treatment, approximately 15 to 20% of patients receiving conventional docetaxel still experience hypersensitivity reactions, with 2 to 4% experiencing severe allergic reactions or anaphylaxis[1]. Severe allergic reactions or anaphylaxis can be life-threatening and are the subject of an FDA “Black Box” warning for Taxotere®.

Starpharma’s DEP® docetaxel is a detergent-free, aqueous formulation that contains no toxic excipients, reducing the risk of hypersensitivity and anaphylaxis. Therefore, it does not require any corticosteroid pre-treatment. There were no cases of hypersensitivity reactions or anaphylaxis reported in the DEP® docetaxel trial program, even without steroid pre-treatment.

Peripheral oedema is also a common and serious side effect of conventional docetaxel treatment (Taxotere®), with 30 to 50% of patients experiencing it despite steroid pre-treatment[1]. However, even in the absence of steroid pre-treatment, only 6.3% of DEP® docetaxel patients experienced peripheral oedema, and the events were mainly mild to moderate (grade 1/2).

DEP® docetaxel treatment was also associated with significantly lower rates (3.8%) of oral mucositis (mouth ulcers) and no cases of severe mucositis. This incidence is much lower than for conventional docetaxel treatment, where these painful events are frequently observed (26% to 53% of patients), with up to 8% of cases experiencing severe mucositis, which can result in the dose reduction, discontinuation or delay of treatment[1].

Moreover, alopecia (hair loss) was notably absent following DEP® docetaxel monotherapy and only 2.5% overall (monotherapy and combination). This distressing side effect is frequently observed (56 to 76% of patients) with conventional docetaxel treatment[1]. In addition, a significant proportion of patients (approximately 10%) treated with Taxotere® regimens have been reported to experience permanent hair loss[4].

Overall, the DEP® docetaxel Phase 2 trial program demonstrated encouraging anti-cancer activity and clinically meaningful responses in a range of difficult-to-treat cancers in heavily pre-treated, advanced, metastatic cancer patients who had failed or progressed on prior therapies. DEP® docetaxel, when used in combination with either nintedanib or gemcitabine, demonstrated particularly encouraging anti-cancer activity in non-small cell lung cancer and pancreatic cancer, respectively. DEP® docetaxel also demonstrated safety and tolerability benefits in key dose-limiting treatment-related adverse events, such as severe neutropenia, compared to published data on conventional docetaxel.

Additional Trial Information

The DEP® docetaxel Phase 2 trial program employed a multi-centre, open-label trial design to assess the safety and, tolerability and preliminary efficacy of DEP® docetaxel in patients with advanced, metastatic solid tumour cancers. The objectives of Phase 2 were to further explore the anti-tumour efficacy of DEP® docetaxel in selected patient cohorts, and to further characterise the safety and tolerability of DEP® docetaxel.

A total of 80 patients with advanced solid tumours were enrolled and treated with DEP® docetaxel as a monotherapy or in combination with nintedanib or gemcitabine. Patients were enrolled across seven trial sites in the UK, including Guy's Hospital London, University College London Hospital (UCLH), St James University Hospital in Leeds, Newcastle Freeman Hospital, The Christie Hospital in Manchester, The Beatson West of Scotland Cancer Centre in Glasgow, and Velindre Cancer Centre in Cardiff.

The Phase 2 trial efficacy and safety outcomes are based on results from 80 enrolled patients with advanced solid cancers. These cancers include pancreatic (N=21), gastro-oesophageal (N=15), lung (small cell and non-small cell; N=21) and small numbers of other advanced, hard-to-treat, rarer cancer types such as cholangiocarcinoma, melanomas, gastro-intestinal tumours, and sarcomas.

DEP® docetaxel was administered intravenously (IV) once every three weeks (Q3W) at either 45 or 60 mg/m^2 docetaxel as a monotherapy or in combination with nintedanib at 200 mg twice daily from day 2 to 21. In the DEP® docetaxel and nintedanib combination arm, only advanced, metastatic non-small cell lung cancer (NSCLC) patients (N=13) were treated, in line with the approved indication for docetaxel and nintedanib (Vargatef®[5]). For the DEP® docetaxel and gemcitabine combination, docetaxel was administered at either 33 or 45 mg/m^2 and 800 or 1000 mg/m^2 gemcitabine; patients received gemcitabine immediately following DEP® docetaxel on Day 1 and Day 8 of the 21 day / 3 weekly (Q3W) dose cycle.

Efficacy was assessed by radiographic imaging (CT [computerised tomography] scans) of tumours evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1). All efficacy response data reported in this announcement are for evaluable patients. Evaluable patients are those that received ≥1 dose cycle of DEP® docetaxel and had a CT scan to assess response to treatment at ≥7 weeks after commencement of treatment with DEP® docetaxel.

Tumour biomarkers, such as CA19-9, were also assessed as a measure of anti-tumour activity, where applicable. Treatment of patients with DEP® docetaxel continued until their disease progressed or worsened, or withdrawal for other reasons (e.g., COVID-19). However, if the treating investigator determined that clinical benefits, such as reduced pain or improved symptoms, were being derived from the treatment, patients had the option to continue treatment beyond disease progression.

All adverse events (AEs) reported for DEP® docetaxel are also reported for conventional docetaxel (Taxotere®).

Almost 90% of treatment-related AEs were mild (grade 1, 57.7%) or moderate (grade 2, 30%), with very few severe (≥ grade 3, 11.5%) events. AEs were generally well tolerated and manageable. The AEs observed (all grades) in ≥10% of all DEP® docetaxel-treated patients in Phase 2 include fatigue (47.5%), nausea (42.5%), vomiting (25.0%), diarrhoea (20.0%), decreased appetite (23.8%), peripheral neuropathy (46.3%), arthralgia (13.8%), myalgia (15.0%), dyspnoea (10.0%) anaemia (10.0%) and thrombocytopenia (11.3%). Note: Patients in this study were heavily pre-treated with other anti-cancer therapies, including platinum drugs, which cause both severe myelosuppression and residual neurological toxicity (PN) and predispose patients to recurrence of these AEs with future treatments.

[5] Vargatef® (Nintedanib) Summary of Product Characteristics, Boehringer Ingelheim, https://www.medicines.org.uk/emc/product/3647/smpc.

About DEP® docetaxel

Developed by Starpharma, DEP® docetaxel is a patented, dendrimer nanoparticle version of the chemotherapy drug docetaxel (Taxotere®[1]), which achieved peak sales of US$3.1B before patent expiry and is widely used for the treatment of a number of common cancers, including lung, gastro-oesophageal, head and neck, breast, and prostate. Unlike conventional docetaxel, DEP® docetaxel is an aqueous formulation, does not contain toxic detergent-like excipients associated with anaphylaxis, and avoids the need for steroid pre-medication. In both preclinical and clinical studies, DEP® docetaxel has demonstrated an improved side effect profile in terms of key adverse events, including myelosuppression, oedema (fluid retention), alopecia (hair loss) and allergic reactions (anaphylaxis/hypersensitivity).

About Starpharma's DEP® platform

Starpharma has developed a unique and valuable delivery platform known as DEP® (Dendrimer Enhanced Product), which utilises dendrimers to improve the effectiveness and safety of conventional and new drugs. DEP® has been widely applied in oncology but also has application to other classes of drugs, such as anti-infectives. DEP® opens new possibilities for more controlled and precisely targeted drug delivery, enhancing therapeutic and commercial opportunities and creating significant optionality. Additionally, the use of DEP® can create new intellectual property and extend the patent life for value-added versions of existing drugs.

Starpharma has developed an impressive pipeline of novel DEP® oncology assets. Its clinical-stage assets, DEP® cabazitaxel, DEP® docetaxel and DEP® irinotecan, are improved versions of commonly used chemotherapeutic drugs that have demonstrated improved anti-cancer effects and safety profiles. Additionally, Starpharma has a promising preclinical pipeline, including DEP® Antibody-Drug Conjugates (ADCs) and DEP® radiotheranostic products. In addition to its internal programs, Starpharma has a number of partnered DEP® programs with global companies, including MSD, Genentech, Chase Sun, and AstraZeneca.

About Starpharma

Starpharma Holdings Limited (ASX: SPL, OTCQX: SPHRY) is a world leader in dendrimer technology for medical applications. As an innovative Australian biopharmaceutical company, Starpharma is focused on developing and commercialising novel therapeutic products that address significant global healthcare needs. Starpharma boasts a strong portfolio of products, partnerships, and intellectual property.

Starpharma's innovative technology is based on proprietary polymers called dendrimers, which are precise, synthetically manufactured, nanoscale molecules. The unique properties of dendrimers – including their size, structure, high degree of branching, polyvalency, and water solubility – are advantageous in medical and pharmaceutical applications.

Starpharma uses its dendrimer technology to develop novel therapeutics and to improve the performance of existing pharmaceuticals. Starpharma's portfolio includes multiple clinical-stage oncology products, which utilise its Dendrimer Enhanced Product ('DEP®') drug delivery technology, and marketed products, including VIRALEZE™ and VivaGel® BV, which utilise SPL7013, a proprietary dendrimer with antimicrobial properties.

Starpharma's DEP® drug delivery platform is being used to enhance the effectiveness of existing and novel therapies and to reduce drug-related toxicities through controlled and specified drug delivery. In addition to Starpharma's internal DEP® programs, Starpharma has multiple DEP® partnerships with international biopharmaceutical companies, including AstraZeneca (oncology), MSD (Antibody-Drug Conjugates), Chase Sun (anti-infectives), and other world-leading pharmaceutical companies. Due to the broad applicability and optionality of Starpharma's DEP® platform, partnered DEP® programs have the potential to generate significant future milestones and royalties.

Starpharma's topical antiviral nasal spray, VIRALEZE™, is now registered in more than 35 countries*, including Europe, the UK, and Asia. Starpharma's novel non-antibiotic vaginal gel, VivaGel® BV, for the treatment of bacterial vaginosis (BV) and prevention of recurrent BV, is registered in more than 50 countries, including in the UK, Europe, Southeast Asia, South Africa, Australia and New Zealand.

For more information about Starpharma, visit www.starpharma.com or connect with Starpharma on LinkedIn.

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Disclosure
This ASX Announcement was authorised for release by the Chair, 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", "outlook", 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 commercialisation 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.