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ASX Announcement

Positive DEP® irinotecan clinical results to be presented at international oncology conference

Highlights

- Positive interim clinical data from Starpharma's Phase 1/2 clinical trial of DEP® irinotecan will be presented at a key international oncology conference that will take place in Boston, US, from 11 to 15 October 2023.
- The data being presented for DEP® irinotecan are in heavily pre-treated, advanced metastatic colorectal cancer (CRC) or platinum-resistant/refractory ovarian cancer patients; these patients had exhausted all available standard-of-care treatments, having received an average of up to 6 prior treatment regimens and 31 cycles. Most of the CRC patients' cancer had continued to grow or spread (progressed) following treatment with conventional irinotecan.
- In summary, DEP® irinotecan demonstrated durable anti-tumour responses in advanced CRC and platinum-resistant/refractory ovarian cancer and was very well tolerated.
- The key DEP® irinotecan results to be presented include:
  - Durable responses for up to 72 weeks in CRC patients receiving DEP® irinotecan monotherapy, with a disease control rate (DCR) of 48%; these responses are particularly positive for these patients who were heavily pre-treated and had exhausted their treatment options, with 97% having progressed after conventional irinotecan treatment;
  - DCR of 100% in CRC patients receiving DEP® irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin (LV), with durable responses of up to 27 weeks to date;
  - DCR of 100% in ovarian cancer patients receiving DEP® irinotecan monotherapy once every two weeks; this cohort of heavily pre-treated patients achieved an objective response rate (ORR) of 29%, which compares favourably to the reported ORR for other treatments (~9-16%) in patients with this stage and category of disease;
  - DEP® irinotecan-treated patients experienced no severe diarrhoea, a problematic adverse event affecting more than 20% of patients treated with conventional irinotecan (Camptosar®) and frequently resulting in hospitalisation; and
  - DEP® irinotecan-treated patients experienced no instances of cholinergic syndrome, a problematic group of adverse events reported in ~47% of patients treated with conventional irinotecan.
  - The results for DEP® irinotecan compare favourably to published data on conventional irinotecan, despite the patients in this study being heavily pre-treated, including with conventional irinotecan.
- Patients and clinicians report significantly improved tolerability and quality of life with DEP® irinotecan, compared to their experience with conventional irinotecan, including Camptosar®.
- These interim results support the promising clinical utility of DEP® irinotecan and its potential for application in both colorectal and platinum-resistant/refractory ovarian cancers.
- Recruitment into the monotherapy arm has been completed, and the combination arm is expected to complete enrolment this month, with top-line Phase 2 results to be announced following the completion of patient treatment and data analyses.

Melbourne, Australia; 13 September 2023: Starpharma (ASX: SPL, OTCQX: SPHRY) today announces positive interim results from its Phase 1/2 clinical trial of DEP® irinotecan will be presented at the upcoming American Association of Cancer Research (AACR), National Cancer Institute (NCI) and European Organisation for Research and Treatment of Cancer (EORTC) International Conference on Molecular Targets and Cancer Therapeutics in Boston, US, from 11 to 15 October 2023.

DEP® irinotecan is a novel, patented, nanoparticle formulation of SN38, the active metabolite of the widely used anti-cancer drug, irinotecan (marketed as Camptosar®), developed using Starpharma's proprietary DEP® technology.

The DEP® irinotecan data being presented include encouraging durable signs of efficacy combined with excellent tolerability not only in the irinotecan-approved indication of advanced metastatic colorectal cancer (CRC), but also in platinum-resistant/refractory ovarian cancer, which represents a new market opportunity. These positive results, including prolonged disease control and significant tumour shrinkage, have been achieved in heavily pre-treated patients who have received an average of up to 6 prior treatment regimens and 31 cycles and exhausted all available treatment options.

The data will be presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics by **Dr Jenny Liu, MD, PhD, FRACP, Medical Oncologist and Principal Investigator** at the Kinghorn Cancer Centre, St Vincent's Hospital in Sydney, who commented on the positive results:

"The results of the DEP® irinotecan trial to date have been very promising for patients with advanced colorectal cancer who have exhausted standard treatment options, with prolonged responses and excellent tolerance of the product, including in patients who could not previously tolerate standard irinotecan or had failed prior therapy.

"Our experience in treating more than 20 patients on the trial to date have shown promisingly low rates of severe gastrointestinal adverse events and absence of cholinergic toxicity, which are both common and problematic side effects of standard irinotecan therapy. I am also getting consistent feedback from several patients in the trial that they far prefer DEP® irinotecan plus 5-FU/LV compared to the standard FOLFIRI regimen, which uses conventional irinotecan.

"In this heavily pre-treated group of CRC patients, prolonged disease control seen with DEP® irinotecan is an excellent outcome and a significant clinical benefit and warrants ongoing development."

Dr Natalie Cook, MBChB, MRCP, PhD, the Principal Investigator of the study, a Medical Oncologist and Clinical Lead for the Manchester Experimental Cancer Medicine Centre at the Christie Hospital and University of Manchester in the UK, commented:

"I am impressed with the data on Starpharma's novel dendrimer formulation of the irinotecan active metabolite, SN38. In our patients, DEP® irinotecan has shown excellent tolerability and very encouraging efficacy.

"Compared to conventional irinotecan, tolerability for DEP® irinotecan is much improved. Based on the trial data, I believe DEP® irinotecan represents a well-tolerated and promising treatment alternative for patients with colorectal cancer, and potentially others, including platinum-resistant ovarian cancer."

DEP® irinotecan interim clinical results in colorectal cancer[1] (CRC)

Advanced metastatic CRC patients enrolled in the monotherapy cohort (N=38) were heavily pre-treated, having received an average of 4 prior treatment regimens and 31 cycles before entering the study. These patients, aged 35 to 78 years, had exhausted all available treatment options. All but one (97%) of the patients had progressed after prior treatment with conventional irinotecan (up to 4 lines) either as monotherapy or in combination. Despite this heavy pre-treatment, DEP® irinotecan monotherapy achieved durable efficacy responses (stable disease [SD] and tumour shrinkage) for up to 72 weeks (~16 months), with disease control in 48% (15/31) of evaluable[2] patients.

DEP® irinotecan is also being evaluated in combination with 5-fluorouracil (5-FU) and leucovorin (LV), which is a standard irinotecan combination regimen used in the treatment of CRC known as "FOLFIRI". In this combination cohort, there are five evaluable CRC patients thus far, with treatment and enrolment ongoing. The DCR[3] achieved in this cohort is 100%, with an ORR[4] of 20%. For comparison, published data in advanced CRC patients for conventional irinotecan plus 5-FU/LV (FOLFIRI) as second-line therapy (i.e., in

[1] Colorectal cancer (CRC) or bowel cancer, is cancer affecting the large intestine and the rectum.
[2] All efficacy response data reported in this announcement are for evaluable patients. Evaluable patients are those that received ≥1 dose cycle of DEP® irinotecan and had a CT scan to assess response to treatment at ≥~8 weeks after commencement of treatment with DEP® irinotecan.
[3] DCR comprises stable disease (SD), partial responses (PR) and complete responses (CR).
[4] ORR comprises PR and CR.

patients less heavily pre-treated than in the current study) reported an ORR of 4%[5]. In the DEP® irinotecan combination cohort, clinicians have reported significant clinical benefit in these heavily pre-treated patients, including durable responses for up to 27 weeks (SD and partial response [PR]) and very good tolerability. Multiple patients have also provided positive feedback about the improved quality of life experienced with DEP® irinotecan compared to conventional irinotecan therapy.

DEP® irinotecan interim clinical results in platinum-resistant/refractory ovarian cancer

In addition to the positive results in CRC patients, DEP® irinotecan demonstrated excellent responses in patients with advanced metastatic ovarian cancer (N=23). These patients were very heavily pre-treated, with an average of ~6 prior treatment regimens and 30 cycles before treatment with DEP® irinotecan. Furthermore, all patients' cancer was resistant or refractory to platinum-based therapies, which are the standard-of-care in ovarian cancer, and patients had exhausted all available standard-of-care treatment options.

DEP® irinotecan monotherapy achieved a DCR of 100% and an ORR of 29% in ovarian cancer patients dosed every 2 weeks (Q2W). The DCR achieved in all ovarian cancer patients (Q2W and Q3W) is 72%, with several patients continuing to receive treatment and experiencing clinical benefit.

DEP® Irinotecan Response Rates in Platinum-Resistant/Refractory Ovarian Cancer Patients

Endpoint	DEP® Irinotecan Dosing Regimen	
	Once every 2 weeks (Q2W) (N=7)	Q2W + Once every 3 weeks (Q3W) (N=18)
DCR	100%	72.2%
ORR	28.6%	16.7%

DCR, disease control rate; ORR, objective response rate

Responses to DEP® irinotecan treatment in these heavily pre-treated ovarian cancer patients have included tumour shrinkage of up to 60%, response durations of up to 36 weeks, and tumour biomarker reductions of up to 98% in more than 75% of patients. Clinical benefits reported by investigators in the study included complete resolution of a patient's debilitating tumour-related ascites and pleural effusion.

DEP® irinotecan's impressive ORR of 29% in these heavily pre-treated patients compares favourably to standard-of-care single-agent therapies for platinum-resistant ovarian cancer, including paclitaxel (Taxol®), topotecan (Hycamtin®), gemcitabine (Gemzar®) or pegylated liposomal doxorubicin (Caelyx®), which report ORRs ranging from ~9 to 16%[6,7,8].

This cohort of patients with platinum-resistant/refractory ovarian cancer represents a significant unmet medical need and a potential expansion of the current market for irinotecan, given conventional irinotecan is not approved for the treatment of ovarian cancer, either alone or in combination.

The anti-tumour activity of DEP® irinotecan, including prolonged disease control in heavily pre-treated CRC and ovarian cancer patients, is encouraging as it demonstrates the promising clinical utility of DEP® irinotecan and its potential for application in colorectal and platinum-resistant/refractory ovarian cancers.

In addition to CRC and ovarian cancer, DEP® irinotecan has also shown encouraging efficacy signals in pancreatic, gastrointestinal and breast cancer patients.

[5] Tournigand et al., FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study, *Clinical Oncology*, 2023;41(19):3469-3477. https://doi.org/10.1200/jco.22.02774
[6] Taxol® (paclitaxel) Injection label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf
[7] Mutch et al., Randomized Phase III Trial of Gemcitabine Compared with Pegylated Liposomal Doxorubicin in Patients with Platinum-resistant Ovarian Cancer, *J Clin Oncol*, 2007;25(19):2811-2818. https://doi.org/10.1200/jco.2006.09.6735
[8] Pujade-Lauraine et al., Bevacizumab Combined with Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial, J Clin Oncol, 2014;32(13):1302-1308. https://doi.org/10.1200/jco.2013.51.4489

Safety and tolerability of DEP® irinotecan

Throughout the study, DEP® irinotecan therapy has been very well tolerated, with significantly fewer severe gastrointestinal treatment-related adverse events (TRAEs) reported compared to published data on conventional irinotecan.

Importantly, DEP® irinotecan therapy resulted in no reports of severe or life-threatening (≥ grade 3) diarrhoea across ~100 patients enrolled in the study. This result is a significant improvement in the side effect profile when compared to conventional irinotecan (Camptosar®) treatment, which is associated with severe or life-threatening diarrhoea in more than 20% of patients[9]. Irinotecan-induced diarrhoea is frequently associated with the discontinuation of treatment and hospitalisation, and can have potentially fatal outcomes.

In patients treated with DEP® irinotecan, either alone or in combination with 5-FU/LV, there have also been no reports of cholinergic syndrome, which occurs in approximately 47% of patients treated with conventional irinotecan[9]. This problematic adverse event involves symptoms such as acute diarrhoea, slow heartbeat, low blood pressure, increased salivation and tears, blurred vision, excessive sweating, flushing, and abdominal cramping.

TRAEs for DEP® irinotecan have been mostly mild/moderate and include nausea, vomiting, fatigue, hair loss, and bone marrow toxicity (myelosuppression). Importantly, there have also been no immune-mediated adverse events with DEP® irinotecan, making it suitable for combination with immune-oncology agents. In addition, no new adverse events were observed with DEP® irinotecan compared to conventional irinotecan.

Gastrointestinal Treatment-Related Adverse Events (TRAE) in CRC Patients Treated with DEP® Irinotecan Monotherapy* versus Camptosar®^ (Conventional Irinotecan)

Treatment	DEP® Irinotecan	Camptosar®	DEP® Irinotecan	Camptosar®
TRAE	Grade 3/4	Grade 3/4	All Grades	All Grades
Diarrhea	**0%**	22%	**33.3%**	84%
Nausea	**2.6%**	12.7%	**71.8%**	70%
Vomiting	**0%**	14%	**30.8%**	62%

*N=38; ^N=316

Dr Jackie Fairley, CEO at Starpharma, said:

"We are pleased to report positive results for DEP® irinotecan, which has shown promising activity and significantly improved tolerability in advanced colorectal cancer and ovarian cancer. The conference in October is a great opportunity to showcase both DEP® irinotecan and the DEP® platform more broadly.

"Starpharma has received consistent feedback from patients and clinicians indicating that DEP® irinotecan represents a better-tolerated treatment option than conventional irinotecan regimens, which are the mainstay chemotherapeutics for colorectal cancer. Advanced colorectal and ovarian cancers both represent significant unmet medical needs. According to the World Health Organisation (WHO), an increase of about 70% in colorectal cancers globally is expected by 2030."

Recruitment into the DEP® irinotecan trial has been completed for the monotherapy arm, with a small number of ovarian cancer patients ongoing. Recruitment of colorectal cancer patients into the combination arm is approaching completion and is expected to complete during September 2023, with top-line Phase 2 results to be released following completion of patient treatment and data analyses. While finalising the enrolment, treatment and analyses of clinical trial results, Starpharma is also engaging in commercial partnership discussions for DEP® irinotecan and other DEP® assets.

[9] Camptosar® (irinotecan) Injection label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020571s048lbl.pdf

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About DEP® irinotecan

DEP® irinotecan is a novel, patented, nanoparticle formulation of SN38, the active metabolite of the widely used anti-cancer drug, irinotecan (marketed as Camptosar®), delivered using Starpharma's proprietary DEP® technology. Camptosar® and all generic forms of conventional irinotecan carry 'black box' warnings mandated by the US Food and Drug Administration (FDA) for both neutropenia and severe diarrhoea, which can be dose-limiting and life-threatening. DEP® irinotecan has not resulted in severe diarrhoea in Phase 2 studies. DEP® irinotecan has patent filings to 2039 and up to an additional five years.

The severe diarrhoea caused by conventional irinotecan results from the production of toxic metabolites during the liver metabolism of irinotecan to SN38. DEP® irinotecan was designed to eliminate the need for liver metabolism, thereby avoiding the production of toxic metabolites.

About Starpharma's DEP® irinotecan Phase 2 clinical trial

Starpharma is evaluating DEP® irinotecan as both a monotherapy and in combination with 5-fluorouracil (5-FU) and leucovorin (LV), which is a standard irinotecan combination regimen used in the treatment of CRC known as "FOLFIRI". The Phase 2 DEP® irinotecan trial is being conducted at multiple sites, including Guy's Hospital in London, Beatson Cancer Centre in Glasgow, Imperial College London, and the Kinghorn Cancer Centre in Sydney.

Clinical and commercial opportunity for DEP® irinotecan

The global colorectal cancer drugs market was valued at ~US$14 billion in 2023 and is forecast to reach more than US$16 billion by 2027[10].

Camptosar® and generic forms of conventional irinotecan are standard-of-care treatments for advanced CRC, with Pfizer's Camptosar® achieving peak sales of ~US$1.1 billion. CRC accounts for approximately 10% of all new cancer diagnoses and is the second leading cause of cancer, affecting more than 1 million people annually, and is the fourth leading cause of cancer-related death.

CRC incidence is increasing markedly among younger age groups, with rates of colon cancer more than doubling in adults aged 20 to 54 since the 1990s. Studies have shown that, compared with adults born around 1950, those born around 1990 have double the risk of colon cancer and quadruple the risk of rectal cancer[11].

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, increasing 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.

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[10] https://www.researchandmarkets.com/report/colorectal-cancer-drug

[11] Siegel et al., Colorectal Cancer Incidence Patterns in the United States, 1974–2013, *JNCI*, 2017;109(8):djw322. https://doi.org/10.1093/jnci/djw322

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 materialise, 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 future performance of any Starpharma product.