ASX Announcement

# DEP irinotecan clinical data presented at AACR meeting

**Melbourne, Australia; 16 October 2023: Starpharma (ASX: SPL, OTCQX: SPHRY)** today provides a copy of the DEP® irinotecan clinical poster, highlighting the recently announced[1] positive interim clinical data from Starpharma's Phase 1/2 clinical trial, which demonstrated durable anti-tumour responses in advanced colorectal cancer (CRC) and platinum-resistant/refractory ovarian cancer.

The poster also includes new positive data for DEP® irinotecan in the platinum-resistant ovarian cancer patient cohort, where the objective response rate (ORR[2]) in patients dosed every 2 weeks (Q2W) has increased from the previously reported 29%[1] to 43%. In addition to this impressive efficacy, the duration of responses to DEP® irinotecan treatment in these heavily pre-treated ovarian cancer patients, with tumour shrinkage of up to 60%, now have durations of up to 45 weeks, compared with 36 weeks reported previously[1]. Several patients with ovarian cancer remain on DEP® irinotecan treatment.

DEP® irinotecan's impressive ORR of 43% in these heavily pre-treated patients compares very 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%[3,4,5].

This DEP® irinotecan poster was presented over the weekend in Boston, US, by **Dr Jenny Liu**, MD, PhD, FRACP, Medical Oncologist and Principal Investigator of the study at the Kinghorn Cancer Centre, St Vincent's Hospital in Sydney, at the International Conference on Molecular Targets and Cancer Therapeutics, co-hosted by the American Association of Cancer Research (AACR), the National Cancer Institute (NCI) and the European Organisation for Research and Treatment of Cancer (EORTC) from 11 to 15 October 2023.

Dr Jenny Liu commented:

> *"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."*

Patients with platinum-resistant/refractory ovarian cancer represent 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.

The poster is appended.

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[1] ASX Announcement dated 13 September 2023: Positive DEP® irinotecan clinical results presentation
[2] ORR = partial responses (PR) + complete responses (CR).
[3] Taxol® (paclitaxel) Injection label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf
[4] Mutch et al., *J Clin Oncol*, 2007;25(19):2811-2818.
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**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 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.

# A Phase 1/2 Study of Dendrimer-Enhanced (DEP®) SN38 (SN38-SPL9111 / DEP® Irinotecan) in Patients with Advanced Solid Tumours

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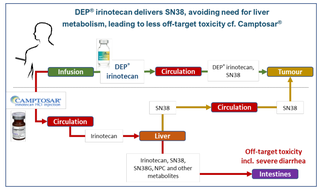
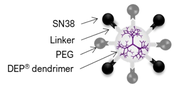
## Background

- DEP® irinotecan, also called DEP® SN38, is a novel, patented, highly water-soluble, poly-L-lysine dendrimer nanoparticle modified with polyethylene glycol (PEG) with SN38 covalently linked via a hydrolysable linker.
- The dendrimer size limits it to circulatory system and, via extravasation through leaky tumour vasculature, they accumulate in tumour tissue providing increased tumour targeting and sustained delivery of cytotoxic drugs[1].
- Irinotecan, widely used in advanced colorectal (CRC) and other gastrointestinal (GI) cancers, is associated with significant cholinergic toxicity and life-threatening diarrhoea, both FDA "Black Box" warnings.
- Irinotecan requires complex conversion in the liver to the active moiety, SN38, with high interpatient plasma levels varying greatly.
- Following encouraging preclinical efficacy of DEP® irinotecan compared with irinotecan (see poster C167), this Phase 1/2 clinical trial was initiated in patients with advanced solid tumours, including CRC and platinum-resistant ovarian cancer.
- Phase 1 objective was to establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of DEP® irinotecan (DEP® SN38). Phase 2 objectives included preliminary efficacy as defined by RECIST v1.1 and serum tumour biomarkers, and further safety and tolerability assessment.




## Methods

- DEP® irinotecan administration: intravenous (IV, ~60 min infusion) dosing once every 14 (Q2W) or 21 (Q3W) days; administered as mg/m² SN38
- 5-FU (fluorouracil)/LV (leucovorin) administration: as per modified De Gramont protocol[2].
- Patients included advanced colorectal, ovarian, breast, pancreas, lung, upper GI cancers.
- Dose was escalated to study the safety profile and identify a recommended phase 2 dose (RP2D / RD) for expansion cohorts.




DEP® Irinotecan nanoparticle ~ 10 - 15 nm

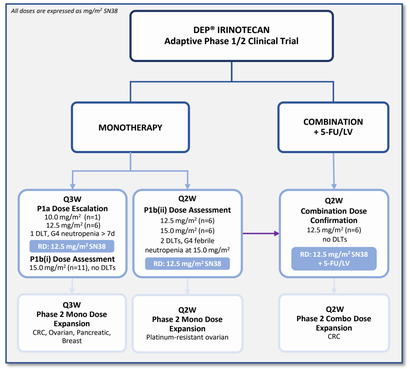
## KEY ELIGIBILITY CRITERIA

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Patients with advanced or metastatic solid tumours, including CRC and platinum resistant high-grade serous ovarian carcinoma (HGSOC)<br>• Measurable or evaluable disease<br>• Eastern Cooperative Oncology Group (ECOG) performance status 0-1<br>• Life expectancy ≥ 12 weeks | • Uncontrolled brain metastases or spinal cord compression<br>• UGT1A1*28 homozygous/congenital deficiency only in Phase 1 cohorts<br>• DPD deficiency by standard genotypic testing for 5-FU/LV combination treatment<br>• History of active bowel obstruction or inflammatory or acute GI disorders with diarrhea as major symptom |

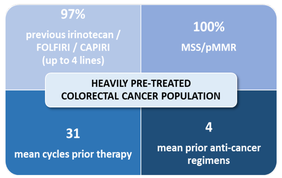
EU Clinical Trials Register EudraCT: 2019-001318-40

## Results

**DEP® IRINOTECAN RECOMMENDED DOSE (RD):** 12.5 mg/m² SN38 MONOTHERAPY and 5-FU/LV COMBINATION THERAPY

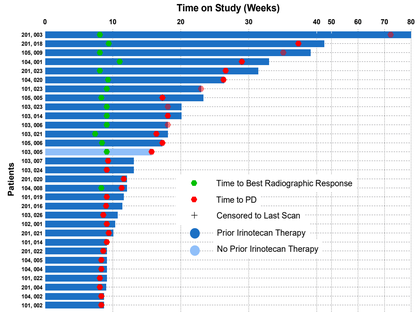



### COLORECTAL PATIENTS OVERVIEW




- 95% had prior cancer surgery; 68% radiotherapy
- **DEP® irinotecan monotherapy**: Mean age: 59 years old (35-78)
- **DEP® irinotecan 5-FU/LV combination therapy**: Mean age: 52 years old (31-77) cohort; ongoing patients including several first assessment CT scans pending

### COLORECTAL PATIENTS: EFFICACY OVERVIEW




### COLORECTAL PATIENTS: EFFICACY OVERVIEW

| Efficacy Response in Evaluable Patients | | |
|---|---|---|
| DEP® irinotecan Monotherapy, Q3W, Q2W (N=38) | RECIST Evaluable, N | 31 |
| | DCR (n) | 48% (15) |
| | ORR (n) | 0% (0) |
| | Duration of response | up to 72 weeks |
| DEP® irinotecan combination with 5FU/LV, Q2W (N=17) | RECIST Evaluable, N | 5 |
| | DCR (n) | 100% (5) |
| | ORR (n) | 20% (1) |
| | Duration of response | up to 35 weeks |

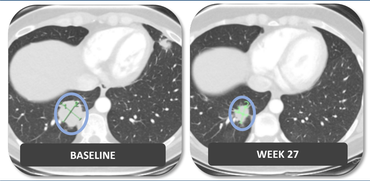
Evaluable: patients who received ≥ 1 dose DEP® irinotecan and a CT scan at ≥ ~Week 8 after first dose.
ORR: Objective Response Rate (CR+PR/ORR evaluable)
DCR: Disease Control Rate (CR+PR+SD/RECIST evaluable)

- Durable efficacy responses of up to 72 weeks for monotherapy and up to 35 weeks after DEP® irinotecan / 5-FU/LV combination therapy *(Note: 12 patients continuing on study treatment, including many pending 1st assessment CT scans)*

### CASE REPORT: 38-year-old woman with Stage IV CRC

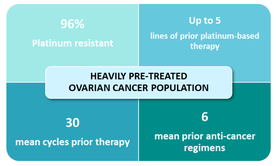
- 2 prior lines of therapy, 16 cycles including irinotecan-based therapy that was very poorly tolerated
- Received DEP® irinotecan (12.5 mg/m² SN38) + 5-FU/LV, Q2W, 17 cycles to date *(Note: patient ongoing in study)*
- Durable anti-tumour response for ~35 weeks, including Partial Response
- 74% reduction in CEA tumour biomarker
- DEP® irinotecan / 5-FU/LV combination treatment extremely well tolerated, especially a distinct lack of severe GI toxicity

**CT Scans of Lung Metastasis (right lower lobe medial)**




**31.3% reduction in target lesion**

### OVARIAN PATIENTS OVERVIEW




- High grade serous ovarian cancer
- 96% had prior cancer surgery; 13% radiotherapy
- **DEP® irinotecan monotherapy**: Mean age: 62 years old (42-74)

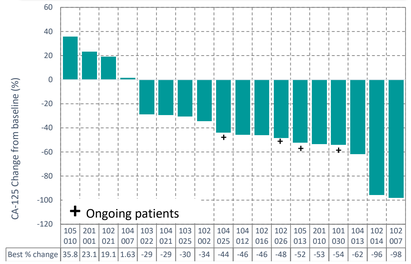
### OVARIAN PATIENTS: EFFICACY OVERVIEW

| Efficacy Response in Evaluable Patients | | Total | Q2W | Q3W |
|---|---|---|---|---|
| DEP® irinotecan Monotherapy | Treated, N | 23 | 8 | 15 |
| | RECIST Evaluable, N | 18 | 7 | 11 |
| | ORR (n) | 22% (4) | 43% (3) | 9% (1) |
| | DCR (n) | 72% (13) | 100% (7) | 55% (6) |
| | Duration of response | up to 45 weeks | up to 45 weeks | ≥ 27 weeks |

Evaluable Patients: patients who received ≥ 1 dose DEP® irinotecan and a CT scan at ≥ ~Week 8 after first dose.
ORR: Objective Response Rate (CR+PR/ORR evaluable)
DCR: Disease Control Rate (CR+PR+SD/RECIST evaluable)

- Durable responses for up to 45 weeks, including 43% ORR and 100% DCR in very heavily pre-treated, platinum-resistant ovarian cancer patients treated with DEP® irinotecan Q2W; compares favorably to standard-of-care agent treatments e.g., paclitaxel, topotecan, gemcitabine, pegylated liposomal doxorubicin, which reported ORRs of ~9 to 16%[4-6] *(Note: patients continuing on study treatment).*
- Up to ~60% reduction in tumour size
- Complete resolution of soft-tissue tumour and tumour-related ascites in a patient with concomitant reduction in CA-125 to near non-measurable levels

### CA-125 biomarker - up to 98% reduction in 75% patients



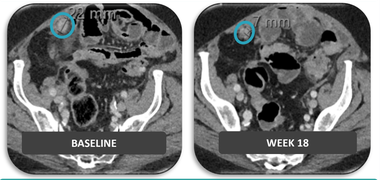

### CASE REPORT: 71-year-old woman with Stage IV HGSOC

- 5 prior lines of therapy and 37 cycles
- DEP® irinotecan monotherapy, Q2W, 12.5mg/m2 SN38 - 12 cycles

*(Note: patient ongoing in study)*

- Efficacy responses:
  - Durable tumour response for > 27 weeks, PR
  - 52% reduction in CA-125 marker

**CT Scans of Metastasis (Peritoneal deposit in RIF)**




**68% reduction in target lesion**

### DEP® IRINOTECAN SAFETY OVERVIEW

DEP® irinotecan treated patients: monotherapy (N= 95) and combination therapy (N=17); > 630 dose cycles administered

- Majority of treatment-related adverse events (TRAEs) mild and moderate
- Significantly fewer ≥ grade 3 (severe) TRAEs compared to (cf.) conventional irinotecan; 11% vs ~53-74% irinotecan monotherapy, 5-FU/LV combination therapy[3]
- No cholinergic symptoms, 0% vs ~47% pts irinotecan
- Neutropenia uneventful; managed with G-CSF
- No new TRAEs with DEP® irinotecan cf. irinotecan
- At least 2 patients have continued DEP® irinotecan treatment through radiologic disease progression due to clinical benefit, and particularly excellent tolerability

| DEP® Irinotecan Treatment-related Adverse Events (% of all TRAEs) | | | |
|---|---|---|---|
| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| 66% | 23% | 8% | 3% |

| Number (%) of Patients with Treatment-Related Adverse Events (most severe event) ≥ 10% patients (N=112) | | | | |
|---|---|---|---|---|
| System Organ Class<br>MedDRA Preferred Term | All Grades n (%) | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) |
| **Blood and Lymphatic System Disorders** | | | | | |
| Anaemia | 34 (30) | 11 (10) | 16 (14) | 7 (6) | |
| Leukopenia | 21 (19) | 8 (7) | 4 (4) | 7 (5) | 2 (2) |
| Lymphopenia | 12 (11) | 6 (5) | 5 (4) | 1 (1) | |
| Neutropenia | 63 (56) | 17 (15) | 8 (7) | 19 (17) | 19 (17) |
| Thrombocytopenia | 19 (17) | 16 (14) | 3 (3) | | |
| **Gastrointestinal Disorders** | | | | | |
| Abdominal pain | 14 (13) | 13 (12) | 1 (1) | | |
| Constipation | 14 (13) | 9 (8) | 5 (4) | | |
| Diarrhoea | 42 (38) | 30 (27) | 12 (11) | | |
| Nausea | 76 (68) | 50 (45) | 24 (21) | 2 (2) | |
| Vomiting | 40 (36) | 32 (29) | 7 (6) | 1 (1) | |
| **General Disorders and Administration Site Conditions** | | | | | |
| Fatigue | 51 (45) | 28 (25) | 19 (17) | 4 (4) | |
| **Investigations** | | | | | |
| Alanine Aminotransferase (ALT) Increased | 19 (17) | 15 (13) | 2 (2) | 2 (2) | |
| Aspartate Aminotransferase (AST) Increased | 20 (18) | 14 (13) | 4 (4) | 2 (2) | |
| Blood bilirubin increased | 12 (11) | 9 (8) | 3 (3) | | |
| **Metabolism and Nutrition Disorders** | | | | | |
| Decreased Appetite | 19 (17) | 13 (12) | 6 (5) | | |
| **Skin and Subcutaneous Tissue Disorders** | | | | | |
| Alopecia | 64 (57) | 24 (21) | 40 (36) | | |
| Rash | 14 (13) | 14 (13) | | | |

| GI toxicity is significantly less severe with DEP® irinotecan e.g., CRC monotherapy treatment | | |
|---|---|---|
| TRAE | DEP® Irinotecan mCRC pts (N=38) | Conventional Irinotecan (Camptosar®)[3] mCRC pts (N=316) |
| | Grade 3 / 4 | Grade 3 / 4 |
| Diarrhea | 0 | 22% |
| Nausea | 2.6% | 12.7% |
| Vomiting | 0 | 14% |

**DEP® irinotecan - well tolerated in UGT1A1*28 homozygous mutant patients who are at risk of increased systemic exposure to SN38**

- 15 UGT1A1*28 patients: DEP® irinotecan monotherapy (12) or combination (3) in Phase 2 dose expansion cohorts
- DEP® irinotecan started at 8 mg/m² SN38, 11 escalated to 10 mg/m² (n=7), and then 12.5 mg/m² (n=4) SN38 to date
- Well tolerated, no significant toxicities, including no severe diarrhea, vomiting or nausea
- Efficacy signals observed in at least 6 patients, including stable disease for ≥ 36 weeks

*(Note: several patients are ongoing in the trial, and pending 1st assessment scan)*

**DEP® IRINOTECAN MONOTHERAPY OR 5-FU/LV COMBINATION THERAPY**

**HIGHLY ENCOURAGING ANTI-TUMOUR ACTIVITY IN HEAVILY PRE-TREATED PATIENTS WITH ADVANCED SOLID TUMOURS**

- Durable anti-tumour responses in CRC, HGS ovarian and other tumour types

**EXCELLENT SAFETY AND TOLERABILITY – SIGNIFICANTLY IMPROVED COMPARED WITH CONVENTIONAL IRINOTECAN**

- Distinct lack of severe GI toxicity, including life-threatening diarrhoea; 0% cf. ~ 20%
- No cholinergic symptoms 0% cf. ~ 47%
- Very well tolerated in patients who could not tolerate conventional irinotecan

**Efficacy responses observed in other tumour types**

| Tumour Type | DCR (SD+PR+CR) | Duration of Response |
|---|---|---|
| Breast (N=5) | 100% | ≥ 63 wks |
| Lung (N=2) | 100% | ≥ 27 weeks |
| Upper gastric (N=4) | 50% | ≥ 18 weeks |
| Pancreatic (N=9) | 44% | ≥ 36 weeks |

## Conclusions

DEP® irinotecan (DEP® SN38) is a novel dendrimer formulation that delivers SN38, irinotecan's active moiety, and exhibits encouraging anti-tumour activity, as well as superior tolerability over conventional irinotecan, with these data supporting further clinical development. These interim results support the promising clinical utility of DEP® irinotecan and its potential for application in both colorectal and platinum-resistant ovarian cancers

## Acknowledgements

We would like to thank the patients and their families, and caregivers, for their participation in this study. Starpharma would like to thank participating investigators and their study team for their support on this study, their dedication to patients, particularly during the challenges attributable to the COVID-19 pandemic.

Study sponsored by Starpharma Pty Ltd, Abbotsford, Australia

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