ASX Announcement

DEP® SN38 Results Showcased at GI Cancer Conference

- *Results from patients with metastatic colorectal cancer (mCRC) deemed exceptional responders in the DEP® SN38 Phase 1/2 clinical trial were presented at a specialist gastrointestinal cancer conference in Brisbane, Australia.*
- *DEP® SN38 demonstrated promising efficacy, with sustained and durable disease control for up to 72 weeks in patients previously treated with irinotecan.*
- *DEP® SN38 exhibited a favourable toxicity profile compared with standard irinotecan, contributing to improved quality of life experiences for these patients.*
- *One patient with platinum-resistant ovarian cancer continues to receive DEP® SN38 treatment, having achieved prolonged disease control for more than 1.7 years.*

Melbourne, Australia; 21 November 2024: Starpharma (ASX: SPL, US OTC: SPHRY), an innovative biotechnology company with two decades of experience in advancing dendrimer technology from the lab to the patient, today shares a copy of a DEP® SN38 scientific poster that was presented at the Australasian Gastro-Intestinal Trials Group (AGITG) Annual Scientific Meeting in Brisbane this week.

The poster presentation highlights the outcomes for five selected patients with advanced metastatic colorectal cancer (mCRC) who participated in the Phase 1/2 clinical trial of DEP® SN38 at The Kinghorn Cancer Centre at St Vincent's Hospital and Garvan Institute of Medical Research in Sydney. These patients were deemed exceptional responders by the study site investigators based on their impressive responses to DEP® SN38 treatment, particularly given their advanced disease and extensive prior treatment.

These heavily pre-treated patients' disease had progressed following prior irinotecan exposure and, in some cases, they had experienced intolerance to irinotecan. Despite these challenges, treatment with DEP® SN38 achieved sustained and durable disease control for up to 72 weeks in this group of patients. One of the patients, treated with DEP® SN38 in combination with 5-fluorouracil (5-FU) and leucovorin (LV), achieved a partial response, with a reduction in the size of their target tumour of more than 30%. Importantly, DEP® SN38 also exhibited an excellent toxicity profile with manageable side effects, leading to improved quality of life experiences for these patients.

The development and presentation of the poster was led by Dr Jordan Cohen, MBBS MMed, Medical Oncology Fellow in the team of Dr Jia (Jenny) Liu, MD PhD FRACP, Medical Oncologist and Principal Investigator of the DEP® SN38 Phase 1/2 clinical study at The Kinghorn Cancer Centre.

Dr Liu commented: "The DEP® SN38 trial results are very exciting. DEP® SN38 in heavily pre-treated, advanced cancer patients demonstrated highly encouraging efficacy results in a range of tumour types, including in colorectal cancer where there is a high unmet need for more efficacious and tolerable treatments. These responses include significant and sustained tumour shrinkage and disease control in patients who have previously been treated with irinotecan.

"DEP® SN38 exhibits excellent tolerability, with a distinct lack of severe gastrointestinal toxicity that is a common and problematic feature of irinotecan treatment. The treatment tolerability demonstrated by Starpharma's DEP® SN38, combined with sustained disease control, has meant that many of our patients, including those who are quite young with advanced colorectal cancer, have been able to

receive long-term treatment and continue to work and engage socially with their peers, which is very important for their quality of life."

DEP® SN38 is a novel, water-soluble dendrimer conjugated to SN38, the topoisomerase I (TOP1) inhibitor and active metabolite of irinotecan. DEP® delivery of SN38 avoids liver metabolism normally required for activation, which helps reduce off-target toxicity that is a feature of standard irinotecan. The DEP® dendrimer nanoparticles are retained in the tumour microenvironment via enhanced permeability and retention, enabling prolonged, targeted delivery of the cytotoxic drug to tumours.

The multicentre, global, Phase 1/2 clinical trial of DEP® SN38 (N=114) has shown promising efficacy in several tumour types, including mCRC and platinum-resistant ovarian cancer, along with highly favourable safety and tolerability, particularly low rates of severe gastrointestinal events and a lack of cholinergic symptoms compared to published data on conventional irinotecan. One patient with platinum-resistant ovarian cancer remains on treatment, having received 45 dose cycles of DEP® SN38 with achievement of prolonged disease control for now more than 1.7 years.

Summary of the DEP® SN38 Efficacy and Safety Results in these Exceptional Responders

- One patient treated with DEP® SN38 + 5-FU/LV combination therapy achieved a partial response, with a reduction in size of their target tumour of more than 30%, and four patients exhibited stable disease, with durable disease control lasting up to 72 weeks.
- Four patients showed a concomitant reduction in the levels of the CEA cancer biomarker of up to 74%.
- Dose-limiting toxicities were observed in one patient, who experienced grade 3 febrile neutropenia that required a dose reduction.
- Neutropenia in other patients was managed effectively with G-CSF[1], and gastrointestinal events were mostly mild to moderate, with only one instance of grade 3 nausea reported, and no cases of severe diarrhoea in any patients.
- Two patients continued treatment beyond progression of their disease due to clinical benefit.

Summary of the Patient Characteristics

- Five patients (2 male, 3 female) with mCRC and median age of 38 years.
- Treatment included either monotherapy with DEP® SN38 or a combination of DEP® SN38 with 5-FU/LV (equivalent to the "FOLFIRI" regimen).
- For these patients, the median number of DEP® SN38 treatment cycles administered was 24.
- The median duration of treatment with DEP® SN38 was 59 weeks.

Colorectal cancer is the second leading cause of cancer-related deaths globally. It is often diagnosed at advanced stages, making treatment options limited. The incidence of CRC is increasing among adults younger than 50, as reflected by the ages of the patients in this study. According to the American Cancer Society (ACS), 20% of colorectal cancer diagnoses in 2019 were in patients under the age of 55. This figure is approximately twice the rate seen in 1995[2] and continues to rise.

Starpharma's DEP® SN38 is a priority candidate for licensing, showing promising Phase 1/2 results in mCRC and platinum-resistant ovarian cancer. Starpharma will meet with key regulators in the coming weeks to discuss potential clinical development pathways for DEP® SN38 aimed at achieving commercialisation.

[1] G-CSF, granulocyte-colony stimulating factor, is a growth factor that stimulates the bone marrow to make more blood cells, and increases the number of some types of white blood cells in the blood

[2] https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2023.pdf

About Starpharma

Starpharma ASX: SPL, OTCQX: SPHRY) is an innovative biotechnology company with two decades of experience in advancing dendrimer technology from the lab to the patient. Our mission is to help patients with significant illnesses, such as cancer, achieve improved health outcomes and quality of life through the application of our unique dendrimer technology.

Dendrimers are precise, synthetically manufactured, nanoscale molecules. Their unique properties—including their size, structure, high degree of branching, polyvalency, and water solubility—are advantageous in medical and pharmaceutical applications.

Starpharma's portfolio of dendrimer-based products includes three clinical-stage DEP® (dendrimer enhanced product) assets, preclinical radiopharmaceutical assets, research collaborations, and three commercially marketed over-the-counter (OTC) products.

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.

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Exceptional Responders in a Phase 1/2 Clinical Trial of Dendrimer-Enhanced (DEP) SN38 (SN38-SPL9111) for the Treatment of Metastatic Colorectal Cancer (mCRC)

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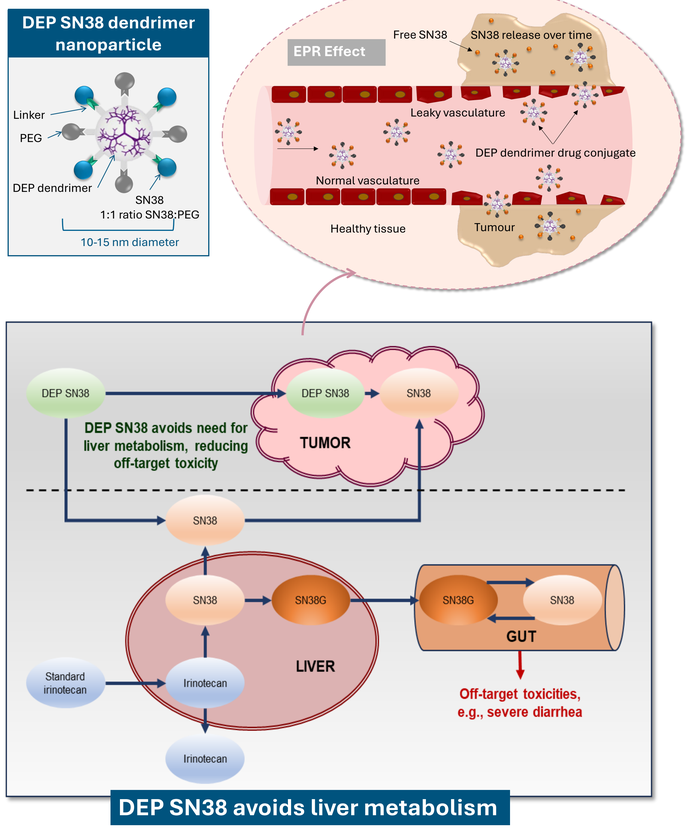
Background

- DEP® SN38 is a novel highly water-soluble, poly-L-lysine dendrimer nanoparticle modified with polyethylene glycol (PEG), with SN38 covalently linked via a hydrolysable linker.
- SN38, the active moiety of irinotecan, is 100-1000-fold more potent than irinotecan[1], but its formation requires complex liver conversion, leading to high interpatient variability in plasma levels[2], which complicates optimal dosing and toxicity management.
- Irinotecan, widely used in metastatic colorectal cancer (mCRC), has significant limitations due to cholinergic toxicity and life-threatening diarrhoea, both FDA "Black Box" warnings[2].



Results

- 17 mCRC patients enrolled at the Kinghorn Cancer Centre: 8 in monotherapy, 9 in 5-FU/LV combination.
- Median of 7 DEP® SN38 cycles given (range 1-25).
- No routine antihistamine, H2 receptor antagonist, or paracetamol required. Majority of patients required no ongoing corticosteroids premedication, or only one day of dosing with dexamethasone.
- Monotherapy: 8 mCRC evaluable with 38% Disease Control Rate (DCR).
- 5-FU/LV combination: 8 mCRC evaluable 75% DCR and **25% Overall Response Rate (ORR)**.

Exceptional Responders of the Kinghorn Cancer Centre

KEY RESULTS	A	B	C	D	E
HISTORY					
Age	54	55	38	38	31
Sex	F	F	M	F	M
Race	White	Asian	White	Other	White
ECOG PS	1	0	0	0	0
Number of prior lines	6	3	5	2	5
Organs involved	Liver, Lung, Node	Liver, Lung, Node	Bone, Liver, Node	Lung	Lung, Node
Prior irinotecan best response	PR	PR	PR	SD but irinotecan intolerance	PR
Surgery / Radiotherapy	Surgery & Radiotherapy	Surgery	Surgery & Radiotherapy	Surgery & Radiotherapy	ND
EFFICACY					
Dose regimen	Q3W Monotherapy 12.5 mg/m^2 SN38	Q2W Monotherapy 15.0 mg/m^2 SN38	Q3W Monotherapy 8.0 mg/m^2 SN38	Q2W 5-FU/LV combination 12.5 mg/m^2 SN38	Q2W 5-FU/LV combination 12.5 mg/m^2 SN38
Number of DEP® SN38 Cycles	24	17	10	25 over 59 weeks	23 over 62 weeks
Best efficacy response	SD	SD	SD	PR	SD
Best % reduction in Target Lesion (TL)	-4.5%	-22.3%	-4.1%	-30.8%	-29.4%
Duration of SD	72 weeks	37 weeks	26 weeks	35 weeks	54 weeks
SAFETY					
Key takeaway	ECOG improved to 0 from Cycle 7 until EOS	DLT at Cycle 1 → reduced to 12.5 mg/m^2 SN38	UGT1A1*28 homozygous mutant → 8 escalated to 12.5 mg/m^2 SN38	G1 GI tox only Many breaks led to PD Treated beyond PD	G1 GI tox only Longer break led to PD Treated beyond PD
Gastrointestinal (GI) toxicities	G3 nausea	G2 nausea G1 vomiting G2 diarrhoea	G1 diarrhoea	G1 nausea G1 diarrhoea G1 constipation	G1 nausea G1 vomiting
Prophylaxis treatment	Anti-emetics from C2 G-CSF from C4	G-CSF at C2-3 only following DLT	None	Anti-emetics from C17 G-CSF D3 each cycle	G-CSF D3 each cycle

Exceptional responders were young, heavily pre-treated and obtained durable control of cancer despite irinotecan pre-treatment – good QoL while on study

DEP® SN38 RECOMMENDED DOSE (RD) → **12.5 mg/m^2 SN38 MONOTHERAPY and 5-FU/LV COMBINATION THERAPY**

All mCRC patients

- Total of 55 mCRC patients across UK & Australia
- 38 in monotherapy, 17 in 5-FU/LV combination
- Median DEP® SN38 cycles = 4 (range 1-29)

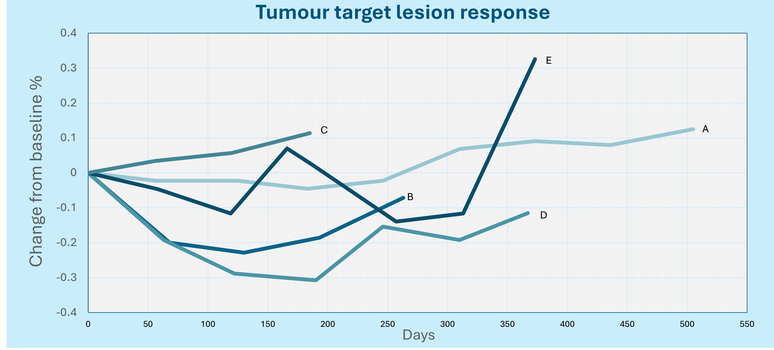
SAFETY

- Majority of TRAEs mild and moderate.
- Neutropenia uneventful; managed with G-CSF.
- No cholinergic symptoms, 0% vs ~47% patients irinotecan.

	Prior lines	RECIST 1.1 Evaluable (n)	DCR (n)	ORR (n)	Duration of response	Median PFS
DEP® SN38 Monotherapy Q3W/Q2W (N=38)	Median = 4 (range 2-9)	31	48% (15)	0% (0)	Up to 72 weeks	2.1 months
DEP® SN38 + 5-FU/LV Combination Q2W (N=17)	Median = 3 (range 2-6)	14	86% (12)	14% (2)	Up to 59 weeks	4.2 months

Evaluable: patients who received ≥ 1 dose DEP® SN38 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).

Tumour target lesion response



Patient at Pre-cycle 12:
"It's crazy I don't get any side effects on this trial. I don't get as much nausea compared to the prior chemotherapy, ..., I have no diarrhoea, and the chemotherapy doesn't affect my QoL."

38-year-old woman with Stage IV CRC

CT Scans of Lung Metastasis

31.3% reduction in target lesion

Methods

- Patients ECOG 0-1 with RECIST v1.1 measurable advanced solid tumours, including mCRC and platinum resistant high-grade serous ovarian carcinoma (HGSOC)[3].
- Open label DEP® SN38 as monotherapy or with 5-FU (fluorouracil)/LV (leucovorin) combination.
- DEP® SN38 administration: intravenous (IV, ~60 min infusion) dosing once every 14 (Q2W) or 21 (Q3W) days; administered as mg/m^2 SN38.
- 5-FU/LV administration: as per modified De Gramont protocol[4].
- Antitumour activity assessed by RECIST v1.1; safety assessed by physical and hematological examinations, and adverse events graded according to CTCAE v5.0.

Conclusion

Exceptional responders

Demonstrate the promising potential of DEP® SN38:

- Durable anti-tumour responses (26-72 weeks)
- Disease controlled with a partial response
- Very well tolerated in a patient who could not tolerate conventional irinotecan
- Excellent tolerability also observed in a UGT1A1*28 homozygous mutant patient who is at risk of increased systemic exposure to SN38
- Improvement of quality of life compared to prior experience of standard of care

All mCRC

- Other exceptional mCRC responders were observed in this study, with disease control of 59 weeks and several of 53 weeks.
- The favorable safety profile without corticosteroid/atropine pre-medication, reduced GI toxicity, and absence of cholinergic symptoms compared to irinotecan, along with the encouraging anti-tumor efficacy, warrant further studies with DEP® SN38 to support its promising clinical utility in mCRC.

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, and 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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Scan for more trial information from ASCO 2024

EU Clinical Trials Register EudraCT: 2019-001318-40