ASX Announcement

HER2-targeted DEP® SN-38 ADC outperforms in HER2+ human cancer model

- **HER2[1] is an important target in a number of different cancers, with antibody-drug conjugates (ADCs) targeting this receptor, including AstraZeneca's marketed Enhertu®, showing significant promise**
- **Starpharma has developed a HER2-targeted DEP® ADC, utilising the active metabolite of irinotecan, SN-38**
- **Starpharma's HER2-targeted DEP® SN-38 ADC outperformed Enhertu®, showing significantly greater anti-tumour activity and improved survival in a HER2+ human cancer xenograft model**

Melbourne, Australia; 26 April 2023: Starpharma (ASX: SPL, OTCQX: SPHRY) today announces that it has developed a HER2-targeted DEP® SN-38 antibody-drug conjugate (ADC), which has shown significant anti-tumour activity in a HER2+ human ovarian cancer xenograft model, outperforming the approved ADC product, Enhertu®[2].

ADCs represent an innovative and growing area of cancer treatment, with encouraging clinical advances and product approvals in recent years. The global ADC market grew from USD ~$5.8 billion in 2021 to USD ~$8.0 billion in 2022 and is projected to reach USD ~$22.9 billion in 2030[3]. HER2 is an important target for cancer treatments, with ADCs targeting this receptor showing significant promise. Currently marketed HER2-targeted ADCs include Kadcyla® (Genentech and Roche) and Enhertu® (AstraZeneca and Daiichi-Sankyo), which is now approved for use in patients with HER2+ or HER2-low metastatic breast cancer, HER2+ metastatic gastric or gastroesophageal junction cancer, and HER2-mutant metastatic non-small-cell lung cancer[4].

Starpharma's HER2-targeted DEP® SN-38 ADC comprises a HER2-directed antibody, trastuzumab, linked to DEP® dendrimers loaded with the topoisomerase I inhibitor, SN-38, which is the active metabolite of irinotecan. Starpharma's HER2-targeted DEP® SN-38 ADC has been designed with a higher drug-to-antibody ratio (DAR), or drug loading, than currently marketed ADCs.

The anti-cancer activity of Starpharma's HER2-targeted DEP® SN-38 ADC was demonstrated in an established HER2+ human cancer xenograft model, utilising the SKOV-3 ovarian cancer cell line that overexpresses HER2. The HER2-targeted DEP® SN-38 ADC and Enhertu®, dosed intravenously (IV) on study days 1, 8 and 15, significantly inhibited tumour growth compared with saline control. The anti-tumour effect of the HER2-targeted DEP® SN-38 ADC was statistically significantly greater than the anti-tumour effect of Enhertu® over the duration of the study ($p<0.0001$). All animals in the HER2-targeted DEP® SN-38 ADC group survived to the end-of-study and survival was statistically significantly greater for the HER2-targeted DEP® SN-38 ADC-treated animals compared with Enhertu® and the saline control group ($p<0.0002$).

Starpharma's HER2-targeted DEP® SN-38 ADC, containing SN-38, achieved superior tumour growth inhibition and survival compared with Enhertu®, despite the active drug in Enhertu®, DXd, being approximately 10 times more potent against topoisomerase I than SN-38[5].

Key advantages of Starpharma's DEP® platform for ADCs include its ability to achieve higher DAR, and therefore higher drug payload, than conventional ADCs (see Table 1, below); its greater flexibility in terms of linker strategies to precisely control drug release profiles; and its ability to widen the therapeutic index of toxic drug payloads. In addition, Starpharma's DEP® platform provides unique flexibility in terms of compatible targeting agents, including biologics (whole antibodies and fragments), small molecules, peptides and other approaches.

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[1] Human epidermal growth factor receptor 2
[2] ENHERTU® is a registered trademark of Daiichi Sankyo Company Limited. Enhertu® comprises the humanised monoclonal antibody/HER2-directed antibody, trastuzumab, covalently linked to a topoisomerase I inhibitor payload, DXd (an exatecan derivative)
[3] https://www.grandviewresearch.com/industry-analysis/antibody-drug-conjugates-market
[4] https://www.enhertu.com
[5] Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. Clin Cancer Res. 2016;22(20):5097-5108. doi:10.1158/1078-0432.CCR-15-2822

Table 1. HER2 ADCs Drug-to-Antibody Ratios (DAR), Drug Payload and Payload Mechanism of Action

HER2 ADC	Approximate Drug-to-Antibody Ratio (DAR)	Drug Payload	Payload Mechanism of Action
Kadcyla® (Genentech/Roche)	3.5	DM-1 (emtansine)	Microtubule inhibitor
Enhertu® (AstraZeneca/Daiichi-Sankyo)	8	DXd (exatecan derivative)	Topoisomerase I inhibitor
HER2-targeted DEP® SN-38 ADC (Starpharma)	13	SN-38	Topoisomerase I inhibitor

Starpharma CEO, Dr Jackie Fairley, said: "Antibody-drug conjugates are one of the fastest growing classes of anti-cancer drugs, with significant progress being made in recent years, including the recent approval and clinical success of Enhertu®, which has shown significant promise in helping patients with HER2+ cancers.

"Starpharma is pleased to report this new data for its internally developed HER2-targeted DEP® SN-38 ADC demonstrating significant anti-tumour activity and survival, compared to Enhertu®, in a HER2+ cancer model.

"Starpharma's DEP® technology delivers a number of advantages in the design of innovative ADCs, including the ability to load more drug payload molecules per construct and having greater flexibility in linker strategies. In addition to our internal activities in this area, Starpharma is delighted to be working in partnership with a number of companies, including MSD, to develop dendrimer-based ADCs using Starpharma's DEP® technology."

Study Methods

Starpharma evaluated the anti-cancer activity of HER2-targeted DEP® SN-38 ADC compared to Enhertu® in an established HER2+ human cancer xenograft model. The study was conducted at the Monash Institute of Pharmaceutical Sciences (MIPS).

This murine xenograft study used the HER2+ SKOV-3 ovarian cancer cell line, in NOD-SCID-Gamma (NSG) immunodeficient mice. The SKOV-3 cell line was chosen because it naturally overexpresses HER2 and is not dependent on estrogen for growth and survival, meaning that it is a robust model for evaluation of HER2-targeting drugs. Tumour cells were inoculated subcutaneously and the resultant tumours were measured 2-3 times weekly using electronic calipers. Tumour volume (mm^3) was calculated at each timepoint.

Following tumour establishment, groups of mice (n = 7-8 per group) were dosed IV on days 1, 8, and 15 as follows:

- Vehicle (saline)
- Control dendrimer-SN-38[6] – 3.28 mg/kg (SN-38 equivalent)
- Enhertu® – 5 mg/kg (total construct dose)[7]
- HER2-targeted DEP® SN-38 ADC – 3.28 mg/kg (SN-38 equivalent)

[6] Control dendrimer-SN-38 = DEP® dendrimer with SN-38 covalently attached (the same dendrimer and linker used to make DEP® SN-38 ADC but lacking the HER2 targeting moiety, *i.e.*, trastuzumab).
[7] In preclinical studies, Enhertu® has been used at doses ranging from 3-10 mg/kg IV. The area under the curve (AUC) in mice at 5 mg/kg Enhertu® is estimated to be comparable with that of Enhertu® in humans at the clinical dosage, and hence 5 mg/kg was selected as the dose for the current study.

Study Results

Effect of HER2-targeted DEP® SN-38 ADC vs. Enhertu® on Tumour Volume Over Time

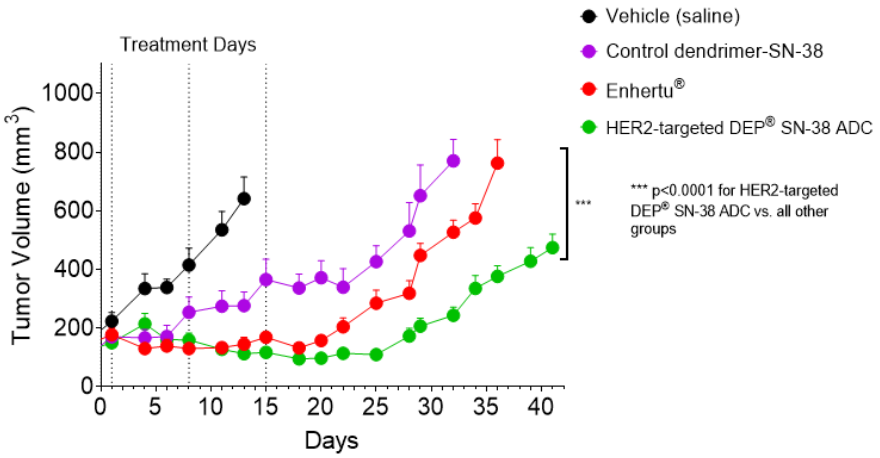

Figure 1. HER2-targeted DEP® SN-38 ADC achieved statistically significantly enhanced tumour growth inhibition compared with Enhertu® or the control dendrimer that lacked the HER2-targeting antibody ($p<0.0001$ for both comparisons). Points and error bars show means ± standard error of the mean (SEM). Statistical analyses used the Mixed Effects Model (GraphPad Prism v9.4.1).

Kaplan-Meier Survival Curve

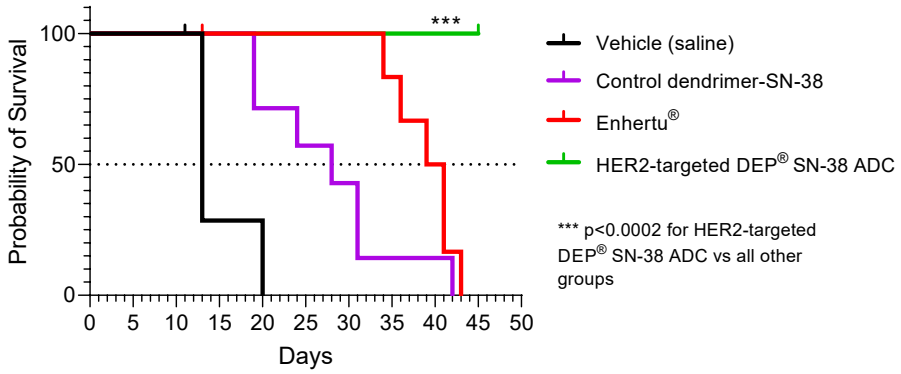

Figure 2. Analysis of survival curves showed significantly enhanced probability of survival of the HER2-targeted DEP® SN-38 ADC group versus all other groups ($p<0.0002$). Probability of survival in the HER2-targeted DEP® SN-38 ADC group was 100% (at end-of-study, 45 days). Median survival, or the time at which probability of survival dropped to 50%, was 40 days for Enhertu®, 28 days for the control dendrimer, and 13 days for the vehicle control. Survival analyses used tumour volume (≥ 1000 mm^3), tumour-site ulceration, or end-of-study as endpoints.

Survival analyses used the logrank (Mantel-Cox) test (GraphPad Prism v9.4.1).

All treatments were well tolerated, as measured by change in body weight over time.

About Starpharma

Starpharma Holdings Limited (ASX:SPL, OTCQX:SPHRY) is a biopharmaceutical company, focussed on the development of pharmaceutical and medical products for unmet patient needs, including in the areas of oncology and infectious diseases.

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 30 countries*, including in Europe, in the UK, and in Southeast Asia. Starpharma's novel non-antibiotic vaginal gel, VivaGel® BV, for treatment of bacterial vaginosis (BV) and prevention of recurrent BV, is registered in more than 45 countries, including in the UK, in Europe, in Southeast Asia, South Africa, Australia and New Zealand.

* Note: VIRALEZE™ is not approved for use or supply in Australia.

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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.