ISRCTN99654100 https://doi.org/10.1186/ISRCTN99654100

# A first-in-human phase I/II study to evaluate the safety, tolerability, anti-cancer activity and metabolism of SN38-SPL9111 (DEP®-SN38), an SN38 dendrimer conjugate, in patients with advanced solid tumours.

**Submission date**
23/12/2024

**Recruitment status**
No longer recruiting

**Registration date**
28/01/2025

**Overall study status**
Completed

**Last Edited**
09/09/2025

**Condition category**
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

Background and study aims
Cancer has a major impact on society and causes significant ill health in those affected by the disease. Cancers that have grown or spread within the body (known as advanced) can generally not be treated by surgery or radiotherapy and require the use of chemotherapy or cytotoxic drugs, which work by killing cells. Chemotherapy drugs may help to slow the spread of the tumours but often cause significant side effects. This research study is a phase I/II first-in-human study being conducted to determine the optimum safe dose
of SN38-SPL9111 (the study drug) in patients with advanced solid tumours. First-in-human means that this research study is the first time that the study drug has been used in people. SN38-SPL9111 or DEP®-SN38 is an investigational new drug which means it has not yet been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) or any other health or regulatory authority. However, it can be used in this type of research study (known as a clinical trial). The study Sponsor, Starpharma, has developed a new method for delivering the active portion (called SN38) of the approved and marketed chemotherapy agent, irinotecan (trade name Camptosar). The delivery method, known as DEP®, is intended to improve the safety and effectiveness of the original drug.

Who can participate?
Patients who have advanced solid tumour cancer which may have spread within the body and current treatments are not working effectively to prevent the spread of disease. Patients whose study doctor thinks they may benefit by taking part in this research study, which is testing a new drug for the treatment of advanced cancers.

What does the study involve?
The study involves firstly reading and understanding the consent document which describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes

the alternative procedures that are available to patients and their right to withdraw from the study at any time. The study doctor will go through the consent document and explain the study to potential patients. Participants are expected to attend all study visits and follow all instructions from their study doctor. During the study, they will not be able to receive other treatments for their disease. Participants will be provided with an emergency card which they should carry with them at all times and show to any healthcare professionals that treat them.

The clinical trial will consist of 4 parts:
1. Phase Ia: Patients will receive increasing doses of the study drug to determine the maximum safe dose that does not cause intolerable side effects.
2. Phase Ib(i), (ii) and (iii): the dose will be further assessed as well as the cycle length (time between successive doses); dosing every 2 weeks and dosing every 3 weeks will be assessed. In Phase Ib(i) and (ii), the study drug will be given to patients on its own (monotherapy) and in Phase Ib(iii), it will be given in combination with 2 other chemotherapy drugs (fluorouracil and leucovorin; combination therapy).
3. Phase I or dose expansion where more patients will be given the dose determined in Phase I to further assess potential side effects of the drug while beginning to look at how efficacious the study drug is in patients with advanced solid tumours.
4. Maintenance part where patients who remain on study treatment and who continue to derive clinical benefit from it while formal analysis of the study data is conducted by the sponsor will continue to receive treatment.
The aims of the study are:
(1) to assess whether the study drug is safe and what are the potential side-effects
(2) to determine the maximum dose at which the study drug can be safely administered without too many side effects
(3) to assess how the body processes and breaks down the study drug
(4) to assess at a preliminary level, how efficacious the study drug is in patients with advanced solid tumours
Patients will continue to receive treatment with the study drug until their cancer worsens or they experience unacceptable side effects or withdraw from the study based on their decision or their doctor’s discretion.

What are the possible benefits and risks of participating?
Benefits: Participants may or may not benefit from their participation in this study. Results may benefit others in the future.
Risks: As this is the first time that the study drug is being used in people, not all of the risks and side effects are known.
Participants may experience some toxicity as a result of the study treatment but every effort will be made to avoid this through careful monitoring by the study doctor. In some cases this toxicity can be serious. The study drug has however been tested in the laboratory and these studies show that the side effects associated with SN38-SPL9111 are similar to those observed following treatment with irinotecan. The study doctor will outline these side effects to potential participants. As the study drug is investigational, when taken alone or in combination with other medications, there may be other risks that are unknown.

Where is the study run from?
The study will be run at 6 study centres, 5 in the United Kingdom and 1 in Australia.

When is the study starting and how long is it expected to run for?
August 2019 to June 2025

Who is funding the study?
Starpharma Pty Ltd, the study sponsor is funding the study.

Who is the main contact?
Dr Stephanie Edmondson, Associate Director, Clinical Development, stephanie.edmondson@starpharma.com

# Contact information

### Type(s)
Principal investigator

### Contact name
Dr Natalie Cook

### ORCID ID
https://orcid.org/0000-0003-2606-1082

### Contact details
The Christie Foundation Trust
Wilmslow Road
Manchester
United Kingdom
M20 4BX
+44 (0) 161 446 3000
natalie.cook17@nhs.net

### Type(s)
Public, Scientific

### Contact name
Dr Stephanie Edmondson

### ORCID ID
https://orcid.org/0009-0004-3274-9427

### Contact details
Starpharma Pty Ltd
4 - 6 Southampton Crescent
Abbotsford
Australia
3067
+61 3 8532 2700
stephanie.edmondson@starpharma.com

# Additional identifiers

### Clinical Trials Information System (CTIS)
2019-001318-40

### Integrated Research Application System (IRAS)
264996

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
SN38-SPL9111-001, CPMS 42308

# Study information

### Scientific Title
A phase I/II dose-escalation study to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of SN38-SPL9111 (DEP®-SN38), an SN38 dendrimer conjugate, in patients with advanced solid tumours.

### Study objectives
The hypothesis is that a poly-lysine dendrimer nanoparticle delivery platform (DEP) can effectively deliver SN38, a topoisomerase 1 inhibitor and the active portion of the anti-cancer drug irinotecan, and demonstrate a potential improvement in irinotecan's clinical utility in patients with advanced solid tumors.

### Ethics approval required
Ethics approval required

### Ethics approval(s)
1. approved 07/08/2019, Yorkshire & The Humber - Leeds East Research Ethics Committee (Health Research Authority Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 0207 1048 088; leedseast.rec@hra.nhs.uk), ref: 19/YH/0188

2. approved 12/05/2020, Bellberry Human Research Ethics Committee (Bellberry Limited) (123 Glen Osmond Road, Eastwood, 5063, Australia; +61 8 8361 3222; bellberry@bellberry.com.au), ref: 2020-03-220

### Study design
Open-label sequential dose-escalation multi-centre study in four parts

### Primary study design
Interventional

### Study type(s)
Treatment, Safety, Efficacy

### Health condition(s) or problem(s) studied
Advanced solid tumours

### Interventions
This is an open-label, sequential dose-escalation study in four parts: (1) dose escalation (Phase Ia), (2) additional monotherapy dose and cycle length assessments (Phase Ib (i) and (ii)) and fluorouracil/leucovorin (5-FU/LV) combination dose assessment (Phase Ib(iii)), (3) dose

expansion (Phase II) and (4) providing ongoing study treatment while conducting formal endpoint analysis of mature data collected for all dosing cohorts (Maintenance part).

In monotherapy Phase Ia and Phase Ib(i) and Ib(ii), DEP-SN38 will be administered either once every 3 weeks (Q3W) or once every 2 weeks (Q2W) at 8, 10, 12.5 or 15 mg/m2 of SN38. In monotherapy Phase II expansion, DEP-SN38 will be administered either Q3W or Q2W at 8 or 12.5 mg/m2 SN38.
In combination therapy with fluorouracil and leucovorin, Phase Ib(iii), DEP-SN38 will be administered Q2W at 12.5mg/m2 SN38. In combination therapy Phase II expansion, DEP-SN38 will be administered Q2W at 8 or 12.5mg/m2 SN38.
DEP-SN38 monotherapy will be administered by intravenous infusion over approximately 60 minutes at a rate of 250 mL/hr using an infusion pump.
Combination therapy was administered to patients in the following order:
1. Leucovorin (350mg) will be administered by intravenous infusion over 60 minutes
2. DEP-SN38 will be administered as above at either 8 or 12.5mg/m2 SN38
3. Fluorouracil will be administered at a bolus dose at 400 mg/m2 and followed by an extended IV infusion at 2400 mg/m2 over 46 hrs.
Treatment duration: For all study phases, treatment will be continued until one of the following criteria applies:
• Disease progression
• Intercurrent illness that prevented further administration of treatment
• Unacceptable adverse event(s)
• Patient decision to withdraw from the study
• Changes in the patient's condition rendered further treatment unacceptable in the judgment of the investigator
• Termination of the study by the Sponsor
Follow-up duration:
Patients withdrawn from the study for unacceptable adverse events will be followed until resolution or stabilization of the event, progression of the disease, or the commencement of another anti-tumour therapy.
Otherwise, patients will have a final safety follow-up at 30 days +/- 7 days after the final dose of DEP-SN38.

## Intervention Type
Drug

## Phase
Phase I/II

## Drug/device/biological/vaccine name(s)
SN38-SPL9111, DEP®-SN38, Fluorouracil, leucovorin

## Primary outcome(s)
The maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of SN38-SPL9111 assessed by monitoring safety through medical review of:
1. Adverse events (AEs) at all study visits; AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
2. Physical examinations and electrocardiogram (ECG) at the screening visit, Day 1 of each dosing cycle, end of treatment visit and at Days 8 and 15 of Cycles 1 and 2,
3. Vital signs assessments at the screening visit, Day 1 of each dosing cycle, end of treatment visit and at Days 2,3, 4, 8 and 15 of Cycle 1 and Days 2,3,8 and 15 of Cycle 2

4. valuation of safety laboratory tests at the screening visit, Day 1 of each dosing cycle, end of treatment visit and at Days 2, 8 and 15 of Cycles 1 and 2

### Key secondary outcome(s))
Safety and Tolerability outcomes measured by:
1. Adverse events (AEs) at all study visits; AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0
2. Physical examinations and electrocardiogram (ECG) at the screening visit, Day 1 of each dosing cycle, end of treatment visit and at Days 8 and 15 of Cycles 1 and 2
3. Vital signs assessments at the screening visit, Day 1 of each dosing cycle, end of treatment visit and at Days 2,3, 4, 8 and 15 of Cycle 1 and Days 2,3,8 and 15 of Cycle 2
4. Evaluation of safety laboratory tests at the screening visit, Day 1 of each dosing cycle, end of treatment visit and at Days 2, 8 and 15 of Cycles 1 and 2

Preliminary efficacy outcomes: measured by computed tomography (CT) scan (with contrast unless contraindicated), magnetic resonance imaging (MRI) scans or applicable radiological assessment for patients of chest, abdomen and pelvis with additional anatomical areas based on the location of known and suspected metastases, as well as signs and symptoms of individual patients. For patients with neurological metastases, the primary imaging modality will be via MRI scans.
Imaging scans will be assessed as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 into the following categories: (1) complete response (CR); (2) partial response (PR); (3) stable disease; or (4) progressive disease.
Scans will be performed at:
• Baseline (within 28 days of first dose)
• Every 9 weeks (+/- 7 days) from the first dose using the same method of assessment used at baseline.

(b) Serum tumour markers applicable to the tumour type will be assayed and changes used to supplement the interpretation of the response.
Tumour markers will be assayed at:
• Screening and
• Pre-dose at each cycle from Cycle 2
Pharmacokinetic outcomes will be measured by determination of the plasma concentrations of free SN38 and total SN38 (free SN38 and SN38-SPL9111) versus time by means of a validated liquid chromatography and tandem mass spectrophotometry (LC-MS/MS) based assay.
PK sampling will occur as below:
• Pre-infusion at Cycles 1, 2 and 3
• Cycle 1: End of infusion and 1, 3, 5, 7, 23, 47 and 71 hours post-end of infusion and also at Day 8 and Day 15 (for Q3W dosed patients only)
• Cycle 2: End of infusion and 1, 3, 5, 7, 23 and 47 hours post-end of infusion and also at Day 15 (for Q3W dosed patients only)

### Completion date
10/04/2025

## Eligibility

### Key inclusion criteria
1. Signed Informed Consent Form.
2. At least 18 years old.

3. Patients with histologically or cytologically confirmed advanced or metastatic cancer for which no standard therapy is available and who, in the opinion of the investigator, could potentially benefit from treatment with irinotecan or SN38-SPL9111. For monotherapy and 5-FU /LV combination therapy, preference will be given to patients with colorectal, pancreatic, ovarian, upper gastrointestinal, and breast cancers. Patients may also be irinotecan naïve. Exceptionally, tumours in other locations may be enrolled subject to sponsor approval.
4. Willing to be tested for uridine diphosphate-glucuronosyl transferase 1 family, polypeptide A1 (UGT1A1) genotype (if this result is not already available).
5. Willing to undergo testing for Dihydropyrimidine dehydrogenase (DPD) deficiency (if this result is not already available); only applicable to patients being considered for the combination treatment part of the study.
6. Measurable disease per RECIST version 1.1.
7. Adequate bone marrow reserve as demonstrated by an absolute neutrophil count (ANC) ≥ 1.5 × 109/L or platelet count ≥ 100 × 109/L (cannot be post-transfusion) or haemoglobin ≥ 9 g/dL (can be post-transfusion).
8. Serum biliruin < 1.5 x upper limit of normal (ULN).
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level < 2.5 × ULN or < 5x ULN for patients with liver metastases.
10. Serum creatinine 1.5 ULN or if creatinine > 1.5 ULN then calculated creatinine clearance must be 50 mL/min (using the Cockcroft-Gault formula).
11. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
12. Life expectancy of greater than 12 weeks.
13. Reproductive inclusion criteria:
13.1. If of childbearing potential, willing to use an effective form of contraception (see below) during chemotherapy treatment and for at least six months thereafter.
Such methods include (if using hormonal contraception this method must be supplemented with a barrier method, preferably male condom):
13.1.1. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
13.1.1.1. oral
13.1.1.2. intravaginal
13.1.1.3. transdermal
13.1.2. progestogen-only hormonal contraception associated with inhibition of ovulation:
13.1.2.1. oral
13.1.2.2. injectable
13.1.2.3. implantable
13.1.3. intrauterine device (IUD)
13.1.4. intrauterine hormone-releasing system (IUS)
13.1.5. bilateral tubal occlusion
13.1.6. vasectomised partner
13.1.7. true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
13.2. Women must have a negative pregnancy test at study entry.
13.3. Men who are truly sexually abstinent when this is in line with the preferred and usual lifestyle of the subject or vasectomized or willing to ensure that their female sexual partners use a highly effective means of contraception (i.e. as outlined in Inclusion criterion 12.a.) for the duration of study therapy and 6 months afterwards. In addition, men must be willing to use a condom during sexual intercourse from the first dose of SN38-SPL9111 until 6 months after their final dose, to protect their partner from exposure to the study drug.

**Participant type(s)**
Patient

**Healthy volunteers allowed**
No

**Age group**
Adult

**Lower age limit**
18 years

**Sex**
All

**Total final enrolment**
114

**Key exclusion criteria**
1. Uncontrolled brain metastases or spinal cord compression. Patients who were treated with surgical resection or radiation therapy completing at least 4 weeks earlier are eligible if they are neurologically stable and have a follow-up Magnetic Resonance Imaging (MRI) scan performed within the previous 4 weeks showing no tumour progression.
2. Patients homozygous for the UGT1A1*28 allele (Gilbert syndrome) or patients with a congenital deficiency of UGT1A1 (Crigler-Najjar syndrome) will be excluded from the Phase I dose escalation/dose assessment parts of the study; they may be enrolled in the Phase II dose expansion parts starting at a reduced dose and incrementing to the full RD, if no excessive toxicity is encountered.
3. Patients with a Dihydropyrimidine dehydrogenase (DPD) deficiency identified by standard genotypic testing for the following gene variants: c. 1905+ 1G>A (rs3918290)DPYD*2A; c. 2846A>T (rs67376798); c.1679T>G (rs55886062)DYPD*13; c.1236G>A/HapB3DPYD (rs56038477); only applicable to patients considered for 5-FU/LV combination treatment. Patients identified as having one or more copies of these variants will be excluded from the combination treatment part of this study. Testing for DPD deficiency must be performed using a validated method which is recommended by local health authorities.
4. History of an untreated bleeding diathesis.
5. Active bowel obstruction, history of inflammatory bowel disease or chronic or acute gastrointestinal disorders with diarrhoea as a major symptom.
6. Allergy/hypersensitivity to irinotecan and SN38-containing preparations, pegylated drugs or other components of study therapy or compounds of similar chemical composition or, if enrolling for the 5-FU/LV combination therapy parts, components of 5-FU or LV or previous significant fluoropyrimidine toxicity.
7.1. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening
7.2. High cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year prior to screening
7.3. New York Heart Association (NYHA) Class III or IV congestive heart failure, unstable cardiac arrhythmias or uncontrolled blood pressure
7.4. Previous fluoropyrimidine-induced or associated cardiac toxicity; only applicable to patients considered for 5-FU/LV combination treatment.
8. Other uncontrolled intercurrent illness, including active infection.

9. Participation in a study of an investigational agent within 30 days prior to first dose of study therapy.
10. Anti-tumour therapy (including chemotherapy, radiation therapy, targeted therapeutics or hormonal therapy) within 28 days or 5-half-lives (whichever is shorter) prior to first dose of study therapy. Palliative radiotherapy will be permitted for non-target lesions provided it is completed 14 days prior to first dose of study drug.
11. Cumulative dose of corticosteroid ≥ 150 mg prednisone (or equivalent doses of corticosteroids) within two weeks of the first IMP administration.
12. Unresolved toxicity from prior anti-tumour therapy, defined as toxicities (excluding alopecia) that have not resolved to < grade 2 or baseline as scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Exceptions may be allowed for stable toxicities after investigator discussion with the Medical Monitor and sponsor.
13. Major surgery within 28 days of first dose of study therapy.
14. Pregnant or breast-feeding females.
15. Concurrent or planned treatment with strong inhibitors of UGT1A1 (e.g. atazanavir, gemfibrozil, indinavir). A 1-week washout period is necessary for patients already on these treatments.
16. Patients receiving anticoagulants other than low molecular weight heparin. Note: Patients can be switched to LMWH prior to first dose of SN38-SPL9111.
17. Any concurrent, clinically significant condition which, in the Investigator's opinion, makes it undesirable for the subject to participate in this study or which would jeopardize compliance with the protocol.
Note: The patient’s overall clinical picture should be considered, and reference made to the applicable SmPC and PI, when considering patients for the 5-FU /LV combination therapy parts of the study and ensuring inclusion and exclusion criteria are complied with.

### Date of first enrolment
24/09/2019

### Date of final enrolment
26/09/2023

## Locations

### Countries of recruitment
United Kingdom

England

Scotland

Australia

### Study participating centre
### The Christie NHS Foundation Trust
550 Wilmslow Road
Withington

Manchester
United Kingdom
M20 4BX

**Study participating centre**
**The Royal Marsden Hospital**
Downs road
Sutton
United Kingdom
SM2 5PT

**Study participating centre**
**Cancer Centre at Guy's, Guys and St Thomas' NHS Foundation Trust**
Great Maze Pond
London
United Kingdom
SE1 9RT

**Study participating centre**
**Northern Cancer Centre, Freeman Hospital, Newcastle-upon-Tyne NHS Foundation**
Freeman Road, High heaton,
Newcastle upon Tyne
United Kingdom
NE7 7DN

**Study participating centre**
**The Beatson West of Scotland Cancer Centre**
1053 Great Western Rd
Glasgow
United Kingdom
G12 0YN

**Study participating centre**
**The Kinghorn Cancer Centre, St Vincent's Hospital**
370 Victoria St
Darlinghurst
Australia
2010

# Sponsor information

**Organisation**
Starpharma (Australia)

**ROR**
https://ror.org/018xv9w84

# Funder(s)

**Funder type**
Industry

**Funder Name**
Starpharma Pty Ltd

# Results and Publications

**Individual participant data (IPD) sharing plan**
The research data has been transcribed from records available within the NHS and can still be used for other research studies subject to applicable privacy regulations, subject to ethical approval as necessary and agreement with the data owners.

**IPD sharing plan summary**
Other

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 01/08/2025 | 14/08/2025 | Yes | No |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |