[redacted]

claudio

A multicentric phase 1/2 trial to evaluate the safety and efficacy of SOT102 as monotherapy and in combination with standard of care treatment in patients with gastric and pancreatic adenocarcinoma

Trial intervention	SOT102
Regulatory agency identifier numbers	EUCT number: 2023-504441-31-00 IND number: 157062 NCT number: NCT05525286
Protocol number	SN201 (CLAUDIO-01)
Phase	1/2
Version	Amendment 5
Date	04Jun2024
Sponsor	SOTIO Biotech a.s.
Legal registered address	Ceskomoravska 2532/19b 190 00 Prague Czech Republic

[redacted]

SIGNATURES/PROTOCOL APPROVAL AND RELEASE SOTIO

We, the undersigned, have read this Protocol and agree that it contains all the necessary information required for the conduct of this clinical trial.

For SOTIO Biotech a.s:

[redacted] *See electronic signature*

Chief Medical Officer

[redacted] *See electronic signature*

Senior Medical Director

[redacted] *See electronic signature*

Senior Statistician

Signature Page for VV-TMF-48612 v1.0

Reason for signing: Approved	Name: [redacted] Role: B Date of signature: 11-Jun-2024 07:34:09 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: S Date of signature: 11-Jun-2024 09:20:45 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: C velopment Date of signature: 11-Jun-2024 09:38:18 GMT+0000

Signature Page for VV-TMF-48612 v1.0

[redacted]

SIGNATURES/PROTOCOL APPROVAL AND RELEASE COORDINATING INVESTIGATOR

I, the undersigned, have read this Protocol and agree that it contains all the necessary information required for the conduct of this clinical trial.

Coordinating investigator:

[redacted]

Josep Tabernero, M.D., Ph.D.

Head, Medical Oncology Department,
Vall d'Hebron University Hospital

Director, Vall d'Hebron Institute
of Oncology

Professor of medicine, UVic-UCC

P. Vall d'Hebron 119-129
08035 Barcelona SPAIN

INVESTIGATOR'S DECLARATION

I have read this Protocol and I agree that it contains all the necessary details for carrying out this clinical trial. I agree to personally conduct or supervise the clinical trial as described in accordance with the relevant current Protocol and within the time designated. I will only make changes after receiving the sponsor's approval, except when necessary to protect the safety, rights, or welfare of patients.

I verify that I am suitably qualified by education, scientific medical training, and experience to conduct the clinical trial. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae.

I will provide the Protocol and all information relating to preclinical and previous clinical experience (e.g., Investigator's Brochure) to all associates, colleagues, and staff assisting in the conduct of this clinical trial. I will discuss the material with them to ensure that they are fully conversant with the Protocol, the medical treatment, and the conduct of the clinical trial, and that they will handle the data and information generated in the clinical trial confidentially. I agree to ensure that they are informed about their obligations in meeting the investigator's commitments listed in this Investigator's Declaration, as delegated and applicable to them.

I agree to personally conduct or supervise the clinical trial in accordance with: i) the current version of the Declaration of Helsinki; ii) the current version of International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (ICH E6); iii) the moral, ethical, and scientific principles that justify medical research; and iv) all relevant national and regional laws and regulations relating to clinical trials and the protection of patients of the country in which the clinical trial will be performed.

I will ensure that an institutional review board (IRB) or independent ethics committee (IEC; in the United States [US])/ethics committee (EC; in the European Union [EU])/equivalent committee (outside the US and EU) that complies with the requirements of national and regional legislation and the Declaration of Helsinki, and that follows the recommendations in ICH E6, will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB/IEC (in the US)/EC (in the EU)/equivalent committee (outside the US and EU) all changes in research activity and all unanticipated problems involving risks to patients or others. Additionally, I will not make any changes in the research without IRB/IEC (in the US)/EC (in the EU)/equivalent committee (outside the US and EU) approval, except where necessary to eliminate apparent immediate hazards to patients.

I agree to inform all patients and associates, colleagues, and staff assisting in the conduct of this clinical trial that the trial intervention(s) are being used for investigational purposes, and I will ensure that the requirements relating to obtaining informed consent and IRB/IEC (in the US)/EC (in the EU)/equivalent committee (outside the US and EU) review and approval are met in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6.

All patients will be informed that they may withdraw from the clinical trial at their discretion at any time. I will use only the information sheet and consent form approved by the sponsor and the IRB/IEC (in the US)/EC (in the EU)/equivalent committee (outside the US and EU) which has reviewed this clinical trial.

I will provide the sponsor with any material written by myself (e.g., clinical trial summary) which is given to the IRB/IEC (in the US)/EC (in the EU)/equivalent committee (outside the US and EU) in support of the application. I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6. I agree to the audit and monitoring procedures that involve verification of clinical trial records against the original records by direct access. In case the source documentation and clinical trial data are kept electronically, I agree to ensure that these comply with the requirements on computerized systems and their validation in line with national and regional legislation and recommendations in ICH E6.

I will retain the trial-related essential documents until the sponsor informs me that these documents are no longer needed but no sooner than the requirements in national and regional legislation.

I certify that any laboratory, excluding the central laboratory (laboratories) appointed for the clinical trial, in which laboratory parameters will be determined, is subject to regular external quality control.

I agree to report to the sponsor adverse events that occur in the course of the clinical trial in accordance with national and regional legislation and the Declaration of Helsinki, and consistent with the recommendations in ICH E6. I have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the trial intervention.

I agree to the collection, processing, transfer, use, and storing of my personal data and details relating to my professional activities for the purposes of the clinical trial by the sponsor and/or by a delegated party (e.g., a contract research organization).

I understand that the (electronic) case report forms and other data pertinent to this clinical trial are the property of the sponsor and are confidential. I will supply the sponsor with the clinical trial data in such a way that the patient's personal information and identity are protected.

I agree to comply with all other requirements regarding obligations of clinical investigators and with all other pertinent requirements in accordance with national and regional legislation and the Declaration of Helsinki. I also agree to follow the recommendations in ICH E6.

Investigator's signature: _____

Date: _____

Printed name: _____

Street address: _____

Telephone number: _____

Other contact information

Full contact details for each investigational site, the sponsor, and key coordinating and operational personnel involved in this clinical trial will be maintained in the Trial Master File and in the Investigator Site File.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Version	**Date**
Amendment 5	04Jun2024
Amendment 4	08Mar2024
Amendment 3	27Apr2023
Amendment 2	01Sep2022
Amendment FR-2	22Jun2022
Amendment BE-2	26May2022
Amendment BE-1	03May2022
Amendment FR-1	26Apr2022
Amendment CZ-1	01Mar2022
Amendment 1	14Jan2022
1	23Nov2021

Change number	Description of change	Rationale for change	Section in Amendment 5
1	The population of Part A and B was narrowed to CLDN18.2-positive patients. Prospective testing from biopsy samples for CLDN18.2 expression on tumors was added.	To allow only CLDN18.2-positive patients to be enrolled in the trial	1.1 Synopsis; 1.2 Schema; 1.3.1 Schedule of activities Part A; 1.3.3 Schedule of activities Part B pancreatic; 1.3.4 Schedule of activities Part C; 1.3.5 Schedule of Activities Part D; 2.1 Trial rationale; 4.1 Overall design; 4.1.2 Part A; 4.1.3 Part B; 4.1.4 Part C; 4.1.5 Part D; 4.2 Scientific rationale for trial design; 5.1.1 Inclusion criteria applicable to all trial parts; 6.1.3 Investigational medical device; 8.6 Tumor biopsy; 8.7 Biomarkers
2	Planned duration of trial was updated	To reflect current eligibility criteria and planned assessments	1.1 Synopsis; 4.4 Trial and site start and closure
3	For patients ongoing in gastric cohort, assessments have been updated to reflect that they are continuing in the trial on SoC and no SOT102 will be administered. Eligibility criteria have been updated to reflect that no new gastric/GEJ cancer patients will be enrolled in the trial.	SOT102 will not be administered to gastric/GEJ cancer patients anymore, nor will new patients be enrolled in this cohort - some assessments do not need to be made or do not need to be made within a related time window	1.3.2 Schedule of activities Part B gastric; 5.1.3 Inclusion criteria specific to Part B; 5.2.3 Exclusion criteria specific to Part B
4	Patient rescreening introduced	To allow patients who are deemed to still benefit from trial participation to be considered for the trial in situations when screening was not possible in the initial period	4.1.2.1 Screening; 4.1.3.1 Screening; 4.1.4.1 Screening; 4.1.5.1 Screening; 5.4 Screen failures
5	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document

TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

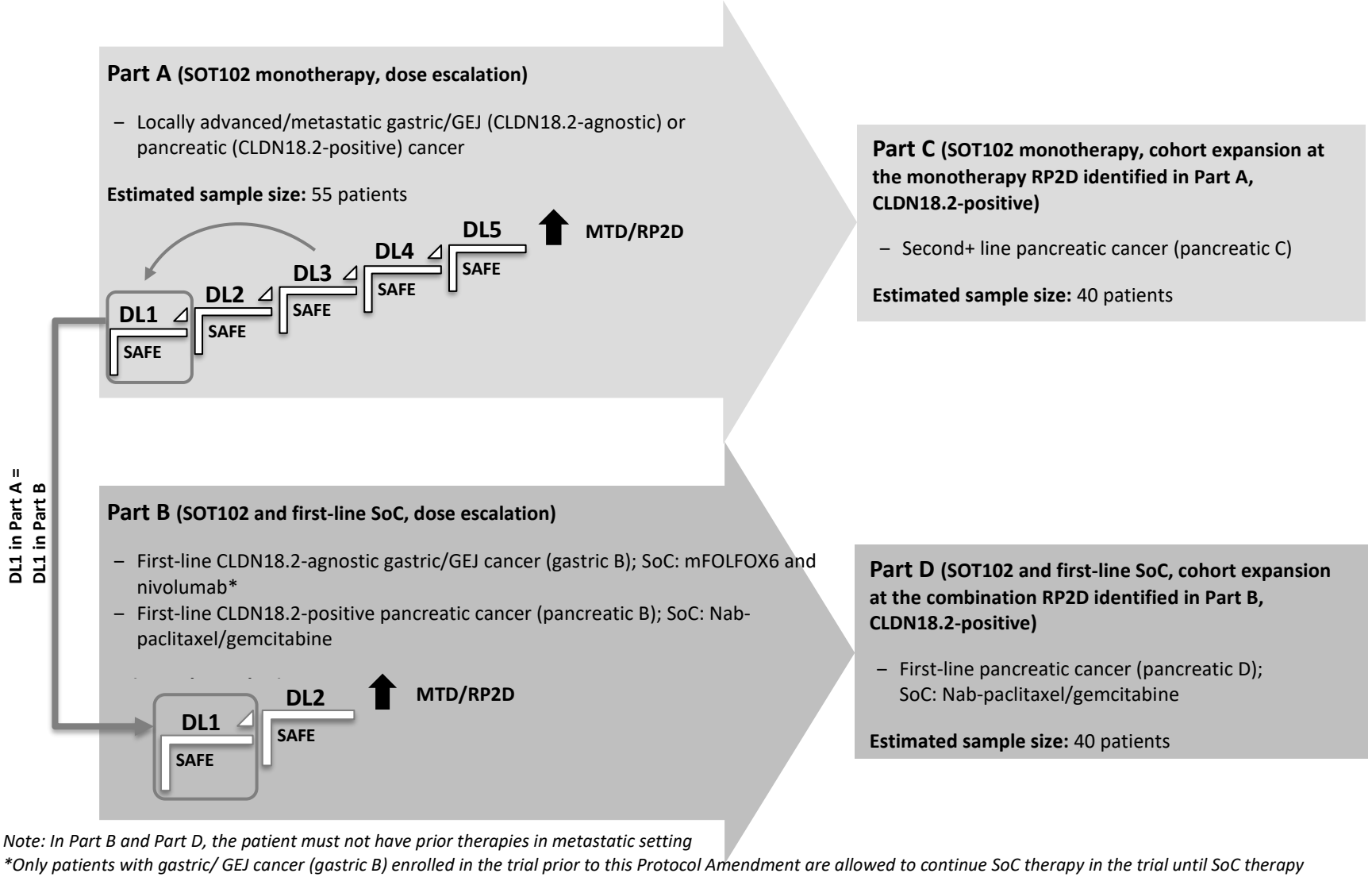
Full trial title	A multicentric phase 1/2 trial to evaluate the safety and efficacy of SOT102 as monotherapy and in combination with standard of care treatment in patients with gastric and pancreatic adenocarcinoma
Regulatory agency identifier numbers	EUCT number: 2023-504441-31-00 IND number: 157062 NCT number: NCT05525286
Rationale	CLDN18.2, splice variant 2 of claudin 18, represents a potentially attractive tumor-associated antigen. In order to make use of the exclusive expression of CLDN18.2 in gastric and pancreatic cells and the fact that transient gastrointestinal toxicity is a manageable adverse event (AE), SOTIO developed SOT102, an antibody-drug conjugate targeting CLDN18.2 with the anthracycline [redacted] as cytotoxic moiety, for the treatment of pancreatic adenocarcinoma. The original intention of the trial was to investigate its objectives in two indications - gastric/GEJ cancer and pancreatic cancer. Following a reassessment of the benefit/risk ratio, it was decided by the sponsor to halt the clinical development in gastric/GEJ cancer for the time being and proceed only with pancreatic cancer. For more details see the IB.
Objectives and endpoints	**Part A and Part B** *Primary* • To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SOT102 given as monotherapy and in combination with first-line standard of care (SoC) treatment. MTD is defined as the highest dose level tested below the dose level associated with ≥33% of dose-limiting toxicity (DLT)-evaluable patients experiencing DLT. The RP2D will be selected based on integrated evaluation of the totality of clinical and preclinical data, for all dose levels tested. *Secondary* • To assess the safety and tolerability of SOT102 in monotherapy and in combination with first-line SoC treatment by the occurrence of DLTs, occurrence of treatment-emergent AEs (TEAEs), SOT102-related AEs, serious AEs (SAEs), AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities • To characterize the pharmacokinetics (PK) of total SOT102, conjugated SOT102, [redacted]

	[redacted] • To explore evidence of SOT102 activity in monotherapy and in combination with first-line SoC treatment in individual patients by anecdotal tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by type and CLDN18.2 expression • To explore whether patients develop any antibodies against SOT102 by the number of patients with detected antibodies against any part of SOT102 **Part C and Part D** *Primary* • To assess the efficacy of SOT102 in monotherapy and in combination with first-line SoC treatment by objective response rate *Secondary* • To evaluate additional measures of efficacy of SOT102 in monotherapy and in combination with first-line SoC treatment by duration of response, progression-free survival per RECIST 1.1, clinical benefit rate per RECIST 1.1 (Part C only), overall survival • To assess the safety and tolerability of SOT102 in monotherapy and in combination with first-line SoC treatment by the occurrence of TEAEs, SOT102-related AEs, SAEs, AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities • To assess quality of life (QoL) after treatment with SOT102 in monotherapy and in combination with first-line SoC treatment by assessment of global and disease-specific QoL by patient-reported questionnaires EORTC QLQ-C30 and EORTC QLQ-PAN26 for patients with pancreatic cancer • To characterize the PK of total SOT102, conjugated SOT102, [redacted] • To explore whether patients develop any antibodies against SOT102 by the number of patients with detected antibodies against any part of SOT102 *Exploratory* • To assess the relationship between the intensity of CLDN18.2 expression and clinical outcome
Trial design	SN201 (CLAUDIO-01) is a multi-modular clinical trial in patients with pancreatic adenocarcinoma whose tumor expresses CLDN18.2 and in ongoing patients with gastric adenocarcinoma or adenocarcinoma of the gastroesophageal junction (GEJ), who were enrolled in the trial prior to this Protocol Amendment and are allowed

	to continue SoC therapy until criteria for discontinuation the SoC therapy are met. The trial combines dose finding of SOT102 in monotherapy (Part A) and in combination with first-line standard of care (SoC) treatment (Part B), followed by respective expansion cohorts (Part C in monotherapy, Part D in combination with first-line SoC treatment). The SoC treatment for pancreatic cancer will be nab-paclitaxel with gemcitabine. The SoC treatment for gastric/GEJ cancer is modified oxaliplatin + leucovorin + 5-fluorouracil containing chemotherapy regimen (mFOLFOX6) with nivolumab.
Trial population	**Part A** Patients with histologically or cytologically confirmed evidence of gastric/GEJ or CLDN18.2-positive pancreatic adenocarcinoma that is advanced or metastatic, who received and/or have been determined to be intolerant of all standard of care therapy known to confer clinical benefit **Part B (separate cohorts for gastric/GEJ and pancreatic cancer)** • Gastric/GEJ adenocarcinoma: Patients with histologically or cytologically confirmed evidence of advanced or metastatic gastric/GEJ adenocarcinoma with human epidermal growth factor receptor 2 (HER2)-negative tumors, who had no earlier treatment for advanced, systemic disease • Pancreatic adenocarcinoma: Patients with histologically or cytologically confirmed evidence of advanced or metastatic CLDN18.2-positive pancreatic adenocarcinoma, who had no earlier treatment for advanced, systemic disease **Part C** • Pancreatic adenocarcinoma: Patients with CLDN18.2-positive tumors who received one or more prior lines of systemic therapy **Part D** • Pancreatic adenocarcinoma: Patients with CLDN18.2-positive tumors and no prior systemic treatment for advanced disease
Interventions	SOT102 will be given once every 14 days via the intravenous route over 45 (±15) minutes. Patients will receive premedication with corticosteroids (4 mg dexamethasone twice daily) the day before, the day of (at least one hour prior), and the day after each SOT102 administration. Nab-paclitaxel (125 mg/m^2) will be given as a 30- to 40-minute infusion followed by gemcitabine (1000 mg/m^2) given as a 30-minute infusion on days 1, 8, and 15. This treatment will be repeated every 28 days. For patients in Part B gastric/GEJ cohort who are continuing on SoC therapy, nivolumab (240 mg) is given as a 30-minute infusion followed by oxaliplatin (85 mg/m^2) given as a 2-hour infusion and

	leucovorin (400 mg/m^2) given as a 30-minute infusion, followed by a 5-fluorouracil bolus of 400 mg/m^2 followed by 2400 mg/m^2 5-fluorouracil given as a 46-hour continuous infusion (mFOLFOX6). This treatment is repeated every 14 days.
Ethical considerations	Based on preclinical toxicology and efficacy studies, it is assumed that the clinical benefits of SOT102 will outweigh the potential risks. More detailed information about the known and anticipated benefits and risks and potential AEs that could be associated with the administration of SOT102 may be found in the IB.
Trial duration	It is expected that active enrollment duration will be 30 months in Part A, 14 months in Part B, 18 months in Part C, and 18 months in Part D. Patients who will respond to therapy will continue with treatment until any of the criteria for treatment discontinuation are met. The planned overall trial duration is approximately 6 years. The trial will end when the last patient completes the last visit or procedure, including follow-up calls.
Estimated sample size	Part A: 55 patients Part B: 32 patients Part C and Part D: 40 patients in each part
Site distribution	Multi-site and multi-regional
Statistical considerations	Each trial part will be analyzed separately following its objectives. Each indication (cohort) in Part B will be analyzed separately. The analyses will be descriptive. No formal testing of statistical hypotheses is planned in this open-label, single-arm trial.
Committees	**Independent committees** A data monitoring committee will be established for trial Part C and Part D to safeguard the interest and safety of the patients participating in the trial and to provide independent review and assessment of the available data in a systematic manner.

1.2 Schema



Note: In Part B and Part D, the patient must not have prior therapies in metastatic setting
**Only patients with gastric/ GEJ cancer (gastric B) enrolled in the trial prior to this Protocol Amendment are allowed to continue SoC therapy in the trial until SoC therapy discontinuation criteria are met.*
DLn, dose level number; GEJ, gastroesophageal junction; mFOLFOX6, modified FOLFOX6; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; SoC, standard of care

1.3 Schedule of activities

1.3.1 Schedule of activities, Part A (SOT102 monotherapy, dose escalation, CLDN18.2-positive)

Visit	Screening		Day -1 of each 14-day cycle	Day 1[a] of each 14-day cycle	Day 2 of each 14-day cycle	Day 8 (±1 day) of each 14-day cycle	Follow-up	
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1					30 (+5) days after the last dose of SOT102	Every 6 weeks (±2 weeks) until disease progression or start of new anticancer therapy
Informed consent[1]	X							
Demography[2]		X						
Cancer[3] **and medical history**		X						
Height		X						
Pregnancy test		X (blood)[4]		Every other cycle before SOT102 administration (urine or blood)			X	
Physical examination		X		X[5]			X	
Body weight and body surface area		X		X[5]			X	
Vital signs[6]		X		X[6]		X	X	
SaO_2		X		X[12]			X	
Clinical chemistry		X[4]		X[5,17]		X	X	
Hematology		X[4]		X[5,17]		X	X	
Coagulation (Quick)		X[4]		X[5,17]			X	
Immunogenicity				X[5,7]			X	
Urinalysis[8]		X[4]		X[5,17]		X	X	
Creatinine clearance[9]		X[4]		X		X	X	
HIV, hepatitis B				X[12] (HIV, HBV-positive patients only)				
ECG		X		X[5,10,12]			X	
LVEF[11]		X[14]		Every 2 months (±2 weeks)			X	
Esophagogastroduodenoscopy		X[14]		X[12]				
ECOG performance status		X		X		X	X	

Visit	Screening		Day -1 of each 14-day cycle	Day 1[a] of each 14-day cycle	Day 2 of each 14-day cycle	Day 8 (±1 day) of each 14-day cycle	Follow-up	
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1					30 (+5) days after the last dose of SOT102	Every 6 weeks (±2 weeks) until disease progression or start of new anticancer therapy
Tumor tissue or cytology sample (FFPE blocks) or unstained slides from archival biopsy or fresh biopsy	X[18]							
Tumor assessment (CT, MRI)[13]		X[14]		Every 6 weeks (±2 weeks) after cycle 1 day 1				
Dexamethasone administration			X	X[5]	X			
SOT102 administration[15]				X				
AEs		X		X		X	X	X[16]
Concomitant medication/non-drug therapies		X		X		X	X	X[16]
Blood and urine for pharmacokinetic studies				X[7]				

a. D1 is the day of SOT102 administration. Patients may be hospitalized for 24 hours on day 1 of cycle 1, cycle 3, and cycle 5 for observation of AEs and PK sampling
1. No trial-specific procedures are to be performed prior to ICF signature
2. Demography includes the collection of information on age at screening, gender, race, and ethnicity
3. Histology/cytology, initial diagnosis date, details about previous systemic and non-systemic treatment together with the associated disease response and date of last disease progression, and any prior mutations/genetic analysis
4. To be done ≤ 7 days prior to day 1 of cycle 1
5. Before SOT102 administration in each cycle
6. Vital signs include body temperature, blood pressure (systolic and diastolic, after ≥15 minutes of rest), and heart rate. To be measured before SOT102 administration, 15 (±5) minutes after the end of SOT102 infusion and 60 (±5) minutes after the end of SOT102 infusion.
7. As specified in section 1.3.6
8. Urine analysis laboratory test other than dipstick must be performed. Entry limit at screening is grade 1 proteinuria (<1 g/24 hours). A test will be performed prior to each day 1 of each cycle and in case of ≥100 mg/dL proteinuria, a 24-hour urine analysis will have to be performed (prior to the start of SOT102 treatment) to document 24-hour proteinuria levels.
9. From serum creatinine, calculated by the Cockcroft-Gault formula; prior to SOT102 administration
10. Within 15 minutes after the end of SOT102 infusion in each cycle; additionally, 24 (±2) hours after the end of SOT102 infusion in cycle 1 and cycle 3
11. Using either echocardiography or nuclear medicine methodology (MUGA scan). However, the method chosen needs to stay the same throughout the trial.
12. As clinically indicated
13. Until disease progression or until the start of a new anticancer therapy. CT will focus on the chest, abdomen, and pelvis.
14. Assessments obtained prior the ICF signature as a part or standard of care/routine practice can be used for screening and trial purposes, provided the timelines for screening and cycle 1 day 1 are met
15. Time to be recorded; starting from cycle 6, SOT102 can be administered on day 1 ±1 day
16. Applicable only for AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment
17. Starting from cycle 2, safety laboratory samples can be collected 1 day early
18. Refer to section 8.6

1.3.2 Schedule of activities, Part B gastric (SOT102 combination with first-line SoC treatment, dose escalation, CLDN18.2-agnostic)

Visit	Day 1 Of each 14-day SoC cycle	Day 8 (±1 day) Of each 14-day SoC cycle	Follow-up Every 6 weeks (±2 weeks) until disease progression or start of new anticancer therapy
Pregnancy test	Every other cycle (urine or blood)[1]		
Physical examination	X[1]		
Body weight and body surface area	X[1]		
Vital signs[2]	X[2]	X	
SaO_2	X[7]		
Clinical chemistry	X[1,10]		
Hematology	X[1,10]	X	
Coagulation (Quick)	X[1,10]		
Immunogenicity	X[1,3]		
Urinalysis	X[1,10]		
Creatinine clearance[4]	X		
HIV, hepatitis B	X[6] (HIV, HBV-positive patients only)		
TSH	Every 6 weeks (±2 weeks), otherwise as per note 6		
ECG	X[6]		
LVEF[5]	Every 2 months (±2 weeks)		
Esophagogastroduodenoscopy	X[6]		
ECOG performance status	X	X	
Tumor assessment (CT, MRI)[7]	Every 6 weeks (±2 weeks) after cycle 1 day 1		
mFOLFOX6 and nivolumab administration[8]	X		
AEs	X	X	X[9]
Concomitant medication/non-drug therapies	X	X	X[9]
Blood and urine for pharmacokinetic studies	X[3]		

1. To be measured in each cycle
2. Vital signs include body temperature, blood pressure (systolic and diastolic, after ≥15 minutes of rest), and heart rate. To be measured in each cycle.
3. As specified in section 1.3.6
4. From serum creatinine, calculated by the Cockcroft-Gault formula
5. Using either echocardiography or nuclear medicine methodology (MUGA scan). However, the method chosen needs to stay the same throughout the trial.
6. As clinically indicated
7. Until disease progression or until the start of a new anticancer therapy. CT will focus on the chest, abdomen, and pelvis.
8. Time to be recorded; starting from cycle 6, SOT102 and/or first-line SoC treatment can be administered on day 1 ±1 day
9. Applicable only for AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment
10. Starting from cycle 2, safety laboratory samples can be collected 1 day early

1.3.3 Schedule of activities, Part B pancreatic (SOT102 combination with first-line SoC treatment, dose escalation, CLDN18.2-positive)

Visit	Screening		Day -1 of each 28-day SoC cycle	Day 1[a,b] Of each 28-day SoC cycle	Day 2 of each 28-day SoC cycle	Day 8 Of each 28-day SoC cycle (±1 day)	Day 15[b] Of each 28-day SoC cycle (±1 day)	Day 21 Of each 28-day SoC cycle (±1 day)	Follow-up	
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1							30 (+5) days after the last dose of SOT102	Every 8 weeks (±2 weeks) until disease progression or start of new anticancer therapy
Informed consent[1]	X									
Demography[2]		X								
Cancer[3] **and medical history**		X								
Height		X								
Pregnancy test		X (blood)[4]		Each cycle (urine or blood)[5]					X	
Physical examination		X		X[5]			X		X	
Body weight and body surface area		X		X[5]			X (weight only)		X	
Vital signs[6]		X		X[6]		X	X[6]	X	X	
SaO_2		X		X[12]					X	
Clinical chemistry		X[4]		X[5,17]		X	X[5,17]	X	X	
Hematology		X[4]		X[5,17]		X	X[5,17]	X	X	
Coagulation (Quick)		X[4]		X[5,17]					X	
Immunogenicity				X[5,7]					X	
Urinalysis[8]		X[4]		X[5,17]		X	X[5,17]	X	X	
Creatinine clearance[9]		X[4]		X		X	X	X	X	
HIV, hepatitis B				X[12] (HIV, HBV-positive patients only)						
ECG		X		X[5,10,12]			X[5,10,12]		X	
LVEF[11]		X[14]		Every 2 months (±2 weeks)					X	
Esophagogastroduodenoscopy		X[14]		X[12]						
ECOG performance status		X		X		X	X	X	X	
Tumor tissue or cytology sample (FFPE blocks) or unstained slides from archival biopsy or fresh biopsy	X[19]									
Tumor assessment (CT, MRI)[13]		X[14]		Every 8 weeks (±2 weeks) after cycle 1 day 1						
Dexamethasone administration			X	X[5]	X		X[18]			
SOT102 administration[15]				X			X			

Visit	Screening		Day -1 of each 28-day SoC cycle	Day 1[a,b] Of each 28-day SoC cycle	Day 2 of each 28-day SoC cycle	Day 8 Of each 28-day SoC cycle (±1 day)	Day 15[b] Of each 28-day SoC cycle (±1 day)	Day 21 Of each 28-day SoC cycle (±1 day)	Follow-up	
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1							30 (+5) days after the last dose of SOT102	Every 8 weeks (±2 weeks) until disease progression or start of new anticancer therapy
Nab-paclitaxel/gemcitabine administration[15]				X		X	X			
AEs		X		X		X	X	X	X	X[16]
Concomitant medication/non-drug therapies		X		X		X	X	X	X	X[16]
Blood and urine for pharmacokinetic studies				X[7]						

a. Patients may be hospitalized for 24 hours on day 1 of cycle 1, cycle 3, and cycle 5 for observation of AEs and PK sampling
b. D1 and D15 are the days of SOT102 administration
1. No trial-specific procedures are to be performed prior to ICF signature
2. Demography includes the collection of information on age at screening, gender, race, and ethnicity
3. Histology/cytology, initial diagnosis date, details about previous systemic and non-systemic treatment together with the associated disease response and date of last disease progression, and any prior mutations/genetic analysis
4. To be done ≤ 7 days prior to day 1 of cycle 1
5. Before SOT102 administration in each cycle
6. Vital signs include body temperature, blood pressure (systolic and diastolic, after ≥15 minutes of rest), and heart rate. To be measured before SOT102 administration, 15 (±5) minutes after the end of SOT102 infusion and 60 (±5) minutes after the end of SOT102 infusion.
7. As specified in section 1.3.6
8. Urine analysis laboratory test other than dipstick must be performed. Entry limit at screening is grade 1 proteinuria (<1 g/24 hours). A test will be performed prior to each day 1 of each cycle and in case of ≥100 mg/dL proteinuria, a 24-hour urine analysis will have to be performed (prior to the start of SOT102 treatment) to document 24-hour proteinuria levels.
9. From serum creatinine, calculated by the Cockcroft-Gault formula; prior to SOT102 administration
10. Within 15 minutes after the end of SOT102 infusion in each cycle; additionally, 24 (±2) hours after the end of SOT102 infusion in cycle 1 and cycle 3
11. Using either echocardiography or nuclear medicine methodology (MUGA scan). However, the method chosen needs to stay the same throughout the trial.
12. As clinically indicated
13. Until disease progression or until the start of a new anticancer therapy. CT will focus on the chest, abdomen, and pelvis.
14. Assessments obtained prior the ICF signature as a part or standard of care/routine practice can be used for screening and trial purposes, provided the timelines for screening and cycle 1 day 1 are met
15. Time to be recorded; starting from cycle 6, SOT102 and/or first-line SoC treatment can be administered on day 1 ±1 day
16. Applicable only for AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment
17. Starting from cycle 2, safety laboratory samples can be collected 1 day early
18. To be done also on day 14 and day 16
19. Refer to section 8.6

1.3.4 Schedule of activities, Part C (SOT102 monotherapy, cohort expansion, CLDN18.2-positive tumors; pancreatic cancer second- or further-line)

Visit	Screening		Day -1 of each 14-day cycle	Day 1[a] Of each 14-day cycle	Day 2 of each 14-day cycle	Follow-up		
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1				30 (+5) days after the last dose of SOT102	Every 6 weeks (±2 weeks) until disease progression or start of new anticancer therapy	Every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until the end of the trial
Informed consent[1]	X							
Demography[2]		X						
Cancer[3] **and medical history**		X						
Height		X						
Pregnancy test		X (blood)[4]		Every other cycle (urine or blood)[5]		X		
Physical examination		X		X[5]		X		
Body weight and body surface area		X		X[5]		X		
Vital signs[6]		X		X[6]		X		
SaO_2		X		X[9]		X		
Clinical chemistry		X[4]		X[5,20]		X		
Hematology		X[4]		X[5,20]		X		
Coagulation (Quick)		X[4]		X[5,20]		X		
Immunogenicity				X[5]				
Urinalysis[7]		X[4]		X[5,20]		X		
Creatinine clearance[8]		X[4]		X		X		
HIV, hepatitis B				X[9] (HIV, HBV-positive patients only)				
ECG		X		X[9]		X		
LVEF[10]		X[11]		X[9]		X		
Esophagogastroduodenoscopy		X[12]		X[9]				
ECOG performance status		X		X		X		
Tumor tissue or cytology sample (FFPE blocks) or unstained slides from archival biopsy or fresh biopsy	X[21]							
Quality of life questionnaire – EORTC		X		X[13]		X		

Visit	Screening		Day -1 of each 14-day cycle	Day 1[a] Of each 14-day cycle	Day 2 of each 14-day cycle	Follow-up		
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1				30 (+5) days after the last dose of SOT102	Every 6 weeks (±2 weeks) until disease progression or start of new anticancer therapy	Every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until the end of the trial
Quality of life questionnaire – EQ-5D-3L		X		X[14]			X[15]	
Tumor assessment (CT, MRI)[16]		X[11]		Every 6 weeks (±2 weeks) after cycle 1 day 1				
Dexamethasone administration			X	X[5]	X			
SOT102 administration[17]				X				
AEs		X		X		X		
Concomitant medication/non-drug therapies		X		X		X		X[18]
Survival information								X
Blood for pharmacokinetic studies				X[19]				

a. D1 is the day of SOT102 administration

1. No trial-specific procedures are to be performed prior to ICF signature
2. Demography includes the collection of information on age at screening, gender, race, and ethnicity
3. Histology/cytology, initial diagnosis date, details about previous systemic and non-systemic treatment together with the associated disease response and date of last disease progression, and any prior mutations/genetic analysis
4. To be done ≤ 7 days prior to enrollment
5. Before SOT102 administration
6. Vital signs include body temperature, blood pressure (systolic and diastolic, after ≥15 minutes of rest), and heart rate. To be measured before SOT102 administration, 15 (±5) minutes after the end of SOT102 infusion and 60 (±5) minutes after the end of SOT102 infusion.
7. Urine analysis laboratory test other than dipstick must be performed. Entry limit at screening is grade 1 proteinuria (<1 g/24 hours). A test will be performed prior to each day 1 of each cycle and in case of ≥100 mg/dL proteinuria, a 24-hour urine analysis will have to be performed (prior to the start of SOT102 treatment) to document 24-hour proteinuria levels.
8. From serum creatinine, calculated by the Cockcroft-Gault formula; prior to SOT102 administration
9. As clinically indicated
10. Using either echocardiography or nuclear medicine methodology (MUGA scan). However, the method chosen needs to stay the same throughout the trial.
11. Assessments obtained prior the ICF signature as a part or standard of care/routine practice can be used for screening and trial purposes, provided the timelines for screening and cycle 1 day 1 are met
12. Up to 6 months before cycle 1 day 1
13. Only in SOT102 cycle 1 and cycle 4
14. Every other SOT102 treatment cycle (starting from cycle 1 day 1)
15. Every 4 months (±2 weeks) until the end of trial (after year 1, every 6 months [±2 weeks] until the end of the trial)
16. Until disease progression or until the start of a new anticancer therapy. CT will focus on the chest, abdomen, and pelvis.
17. Time to be recorded; starting from cycle 2, SOT102 can be administered on day 1 ±1 day
18. After 30 days after the last dose of SOT102, only further-line therapies are collected
19. As specified in section 1.3.7
20. Starting from cycle 2, safety laboratory samples can be collected 1 day early
21. Refer to section 8.6

1.3.5 Schedule of activities, Part D pancreatic (SOT102 combination with first-line SoC treatment, cohort expansion, CLDN18.2-positive tumors; pancreatic cancer first-line)

Visit	Screening		Day -1 of each 28-day SoC cycle	Day 1[a] Of each 28-day SoC cycle	Day 2 of each 28-day SoC cycle	Day 8 Of each 28-day SoC cycle (±1 day)	Day 15[a] Of each 28-day SoC cycle (±1 day)	Day 21 Of each 28-day SoC cycle (±1 day)	Follow-up		
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1							30 (+5) days after the last dose of SOT102	Every 8 weeks (±2 weeks) until disease progression or start of new anticancer therapy	Every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until the end of the trial
Informed consent[1]	X										
Demography[2]		X									
Cancer[3] **and medical history**		X									
Height		X									
Pregnancy test		X (blood)[4]		Each cycle (urine or blood)[5]					X		
Physical examination		X		X[5]			X		X		
Body weight and body surface area		X		X[5]			X (weight only)		X		
Vital signs[6]		X		X[6]		X	X[6]	X	X		
SaO_2		X		X[9]					X		
Clinical chemistry		X[4]		X[5,20]			X[5,20]		X		
Hematology		X[4]		X[5,20]		X	X[5,20]	X	X		
Coagulation (Quick)		X[4]		X[5,20]					X		
Immunogenicity				X[5]							
Urinalysis[7]		X[4]		X[5,20]			X[5,20]		X		
Creatinine clearance[8]		X[4]		X			X		X		
HIV, hepatitis B				X[9] (HIV, HBV-positive patients only)							
ECG		X		X[9]			X[9]		X		
LVEF[10]		X[11]		X[9]					X		
Esophagogastroduodenoscopy		X[12]		X[9]							
ECOG performance status		X		X		X	X	X	X		

Visit	Screening		Day -1 of each 28-day SoC cycle	Day 1[a] Of each 28-day SoC cycle	Day 2 of each 28-day SoC cycle	Day 8 Of each 28-day SoC cycle (±1 day)	Day 15[a] Of each 28-day SoC cycle (±1 day)	Day 21 Of each 28-day SoC cycle (±1 day)	Follow-up		
	21 days before day 1 of cycle 1	Within 21 days before day 1 of cycle 1							30 (+5) days after the last dose of SOT102	Every 8 weeks (±2 weeks) until disease progression or start of new anticancer therapy	Every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until the end of the trial
Tumor tissue or cytology sample (FFPE blocks) or unstained slides from archival biopsy or fresh biopsy	X[22]										
Quality of life questionnaire – EORTC		X		X[13]					X		
Quality of life questionnaire – EQ-5D-3L		X		X[14]						X[15]	
Tumor assessment (CT, MRI)[16]		X[11]		Every 8 weeks (±2 weeks) after cycle 1 day 1							
Dexamethasone administration			X	X[5]	X		X[21]				
SOT102 administration[17]				X			X				
Nab-paclitaxel/gemcitabine administration[17]				X		X	X				
AEs		X		X		X	X	X	X		
Concomitant medication/non-drug therapies		X		X		X	X	X	X		X[18]
Survival information											X
Blood for pharmacokinetic studies				X[19]							

a. D1 and D15 are the days of SOT102 administration
1. No trial-specific procedures are to be performed prior to ICF signature
2. Demography includes the collection of information on age at screening, gender, race, and ethnicity
3. Histology/cytology, initial diagnosis date, details about previous systemic and non-systemic treatment together with the associated disease response and date of last disease progression, and any prior mutations/genetic analysis
4. To be done ≤ 7 days prior to enrollment
5. Before SOT102 administration
6. Vital signs include body temperature, blood pressure (systolic and diastolic, after ≥15 minutes of rest), and heart rate. To be measured before SOT102 administration, 15 (±5) minutes after the end of SOT102 infusion and 60 (±5) minutes after the end of SOT102 infusion.
7. Urine analysis laboratory test other than dipstick must be performed. Entry limit at screening is grade 1 proteinuria (<1 g/24 hours). A test will be performed prior to each day 1 of each cycle and in case of ≥100 mg/dL proteinuria, a 24-hour urine analysis will have to be performed (prior to the start of SOT102 treatment) to document 24-hour proteinuria levels.
8. From serum creatinine, calculated by the Cockcroft-Gault formula; prior to SOT102 administration
9. As clinically indicated
10. Using either echocardiography or nuclear medicine methodology (MUGA scan). However, the method chosen needs to stay the same throughout the trial.
11. Assessments obtained prior the ICF signature as a part or standard of care/routine practice can be used for screening and trial purposes, provided the timelines for screening and cycle 1 day 1 are met
12. Up to 6 months before cycle 1 day 1
13. Only in SOT102 cycle 1 and cycle 4
14. Every other SOT102 treatment cycle (starting from cycle 1 day 1)
15. Every 4 months (±2 weeks) until the end of trial (after year 1, every 6 months [±2 weeks] until the end of the trial)
16. Until disease progression or until the start of a new anticancer therapy. CT will focus on the chest, abdomen, and pelvis.
17. Time to be recorded; starting from cycle 2, SOT102 can be administered on day 1 ±1 day
18. After 30 days after the last dose of SOT102, only further-line therapies are collected
19. As specified in section 1.3.7
20. Starting from cycle 2, safety laboratory samples can be collected 1 day early
21. To be done also on day 14 and day 16
22. Refer to section 8.6

1.3.6 PK and ADA sampling (SOT102), Part A and Part B

All attempts should be made to collect the samples on time. Missed sample collections are considered Protocol deviations. The numbers in parentheses are the expected blood/urine sampling volumes in mL. Patients may be hospitalized for 24 hours in cycles 1, 3, and 5 for collection of PK samples.

An additional PK sample must be collected at the occurrence of any grade ≥3 AE or an intolerable persistent grade 2 AE after the DLT evaluation period in Part A and Part B and at the time (pre-dose) when these events have resolved and SOT102 treatment is resumed. In particular, a PK sample must be collected in the event of a grade 4 AE leading to permanent discontinuation of SOT102.

Purpose	Cycle	Day of cycle	Time point (pre-dose or time after the end of SOT102 infusion)	SOT102 PK	
				Part A	Part B
PK analytes PK parameters - blood	1	1	Cycle 1 day 1 pre-dose	X (5)	X (5)
	1	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	1	1	3 hours (±15 minutes)	X (5)	X (5)
	1	1	6 hours (±15 minutes)	X (5)	X (5)
	1	2	24 hours (±2 hours)	X (5)	X (5)
	1	4	72 hours (±2 hours)	X (5)	X (5)
	1	5	Day 5	X (5)	X (5)
	1	8	Day 8	X (5)	X (5)
	1	11	Day 11	X (5)	X (5)
	1	15	Day 15 (in case cycle 2 day 1 is postponed)	X (5)	X (5)
	2	1	Cycle 2 day 1 pre-dose (can be replaced by sample collected on day 15 unless cycle 2 day 1 is postponed)	X (5)	X (5)
	2	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	3	1	Cycle 3 day 1 pre-dose	X (5)	X (5)
	3	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	3	1	3 hours (±15 minutes)	X (5)	X (5)
	3	1	6 hours (±15 minutes)	X (5)	X (5)
	3	2	24 hours (±2 hours)	X (5)	X (5)
	3	4	72 hours (±2 hours)	X (5)	X (5)
	3	5	Day 5	X (5)	X (5)
	3	8	Day 8	X (5)	X (5)
	3	11	Day 11	X (5)	X (5)
	3	15	Day 15 (in case cycle 4 day 1 is postponed)	X (5)	X (5)
	4	1	Cycle 4 day 1 pre-dose (can be replaced by sample collected on day 15)	X (5)	X (5)
	4	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	5	1	Cycle 5 day 1 pre-dose	X (5)	X (5)
	5	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	5	1	3 hours (±15 minutes)	X (5)	X (5)
	5	1	6 hours (±15 minutes)	X (5)	X (5)

Purpose	Cycle	Day of cycle	Time point (pre-dose or time after the end of SOT102 infusion)	SOT102 PK	
				Part A	Part B
	5	2	24 hours (±2 hours)	X (5)	X (5)
	5	4	72 hours (±2 hours)	X (5)	X (5)
	5	5	Day 5	X (5)	X (5)
	5	8	Day 8	X (5)	X (5)
	5	11	Day 11	X (5)	X (5)
	5	15	Day 15 (can be collected prior to cycle 6 day 1 if timing matches the desired schedule)	X (5)	X (5)
	Additional PK sample to be collected at the time of occurrence of grade ≥3 AE, at the time SOT102 treatment resumes, and at the time of occurrence of grade 4 AE			X (5)	X (5)
	Additional PK sample to be collected in conjunction with ADA sample at the time of disease progression (clinical or radiological per RECIST 1.1) **			X (5)	X (5)
PK concentrations - urine	1	1	Up to 24-hour collection (starting cycle 1 day 1 pre-dose)*	X (approx. 50)	X (approx. 50)
ADA assessment**	1	1	Cycle 1 day 1 pre-dose	X (5)	X (5)
	1	15	Day 15	X (5)	X (5)
	2	1	Cycle 2 day 1 pre-dose (can be collected together with day 15 sample unless cycle 2 day 1 is postponed)	X (5)	X (5)
	3	1	Cycle 3 day 1 pre-dose	X (5)	X (5)
	3	15	Day 15 (in case cycle 2 day 1 is postponed)	X (5)	X (5)
	4	1	Cycle 4 day 1 pre-dose (can be replaced by sample collected on day 15)	X (5)	X (5)
	-	-	Every 2 months in subsequent cycles	X (5)	X (5)
	-	-	30 days after the last dose of SOT102	X (5)	X (5)
	Additional ADA sample to be collected at the time of disease progression (clinical or radiological per RECIST 1.1) **			X (5)	X (5)

*Exact time points will be specified in the Laboratory Manual
**This sample can be substituted by regular sampling, if performed within ±14 days of the disease progression.

1.3.7 PK and ADA sampling (SOT102), Part C and Part D

All attempts should be made to collect the samples on time. Missed sample collections are considered Protocol deviations. The numbers in parentheses are the expected blood/urine sampling volumes in mL. In Part C and Part D, sparse PK sampling will be performed to allow for population PK modeling and exposure-response analysis in order to facilitate dose selection for further trials. The exact time points will be based on an analysis of PK parameters in parts A and B and will at least include the below time points.

An additional PK sample must be collected at the occurrence of any grade ≥3 AE or an intolerable persistent grade 2 AE after the first cycle in Part C and Part D and at the time (pre-dose) when these events have resolved and SOT102 treatment is resumed. In particular, a PK sample must be collected in the event of a grade 4 AE leading to permanent discontinuation of SOT102.

Purpose	**Day of each cycle**	**Time point (pre-dose or time after the end of SOT102 infusion)**	**SOT102 PK**	
			Part C	**Part D**
PK analytes **PK parameters - blood**	1	Day 1 pre-dose	X (5)	X (5)
	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	8	Day 8	X (5)	X (5)
	Additional PK sample to be collected at the time of occurrence of grade ≥3 AE, at the time SOT102 treatment resumes, and at the time of occurrence of grade 4 AE		X (5)	X (5)
	Additional PK sample to be collected in conjunction with ADA sample at the time of disease progression (clinical or radiological per RECIST 1.1) **		X (5)	X (5)
ADA assessment*	1	Day 1 pre-dose	X (5)	X (5)
	1	Within 15 minutes after end of SOT102 infusion	X (5)	X (5)
	Additional ADA sample to be collected at the time of disease progression (clinical or radiological per RECIST 1.1) **		X (5)	X (5)

*Exact time points will be specified in the Laboratory Manual
**This sample can be substituted by regular sampling, if performed within ±14 days of the progression.

2 INTRODUCTION

2.1 Trial rationale

CLDN18.2, splice variant 2 of claudin 18, represents a potentially attractive tumor-associated antigen. In order to make use of the exclusive expression of CLDN18.2 in gastric and pancreatic cells and the fact that transient gastrointestinal toxicity is a manageable adverse event (AE), SOTIO developed SOT102, an antibody-drug conjugate (ADC) targeting CLDN18.2 with the anthracycline [redacted] as cytotoxic moiety for the treatment of CLDN18.2-positive pancreatic adenocarcinoma. SOT102 was potent in killing of CLDN18.2-positive tumor cells *in vitro* and inhibited tumor growth *in vivo*. These findings offer preclinical proof-of-principle that SOT102 is highly specific and potent and warrant exploration in a clinical trial.

The original intention of the trial was to investigate its objectives in two indications - gastric/GEJ cancer and pancreatic cancer. Following a reassessment of the benefit/risk ratio, it was decided by the sponsor to halt the clinical development in gastric/GEJ cancer for the time being and proceed only with pancreatic cancer. For more details see the IB.

2.2 Background

Despite recent advances in the treatment of many types of cancer, the prognosis of gastric and pancreatic adenocarcinomas remains disappointing. Each year, gastric cancer is diagnosed in over one million people worldwide.[1] The disease is only rarely cured[2,3] and has a high case fatality rate.

With approximately 500,000 new cases each year worldwide, pancreatic cancer is not as prevalent as gastric cancer, but it is one of the most lethal tumors.[1] Pancreatic surgery of resectable disease and chemotherapy with a combination of folinic acid (leucovorin), 5-fluorouracil (5-FU), irinotecan, and oxaliplatin; gemcitabine monotherapy; gemcitabine and erlotinib; gemcitabine and capecitabine, or gemcitabine plus albumin-bound paclitaxel with or without chemoradiation are the current treatments for the different stages of pancreatic cancer, but their outcomes are dismal. About 92% of patients with pancreatic cancer die within 5 years of their diagnosis.[4]

Limited treatment options are available for patients with metastatic pancreatic cancer, where the existing second-line therapy has only a modest treatment effect in such patients.[5] Therefore, there is a high unmet medical need for therapeutic options in patients with pancreatic cancer who are eligible for treatment with advanced lines.

The current standard of care (SoC) for first-line treatment of advanced pancreatic cancer is dependent on disease stage and the patient's performance status. Gemcitabine as monotherapy or in combination with various other agents is often the first choice for treatment of this disease. Paclitaxel protein-bound (nab-paclitaxel)/gemcitabine was recently approved for first-line treatment of metastatic pancreatic cancer. Nab-paclitaxel plus gemcitabine led to a significant improvement in survival.[6] Therefore, the nab-paclitaxel plus gemcitabine regimen has been selected as an appropriate choice for first-line treatment of advanced pancreatic cancer, which will be explored in Part B and in Part D.

With treatment options in the first-line setting in gastric/GEJ and pancreatic cancers well-established, the development of SOT102 in this setting required a combination therapy.

Modified oxaliplatin + leucovorin + 5-FU containing chemotherapy regimen (mFOLOFOX6) regimen has been shown to demonstrate comparable efficacy with another standard of care (SoC) treatment in patients with advanced gastric/GEJ cancer, while showing more favorable safety profile with less non-hematologic toxicities.[7] mFOLFOX6 treatment is widely accepted and also recommended by the European Society for Medical Oncology guidelines.[2] Recently, nivolumab in combination with mFOLFOX6 has been approved in the US and in the EU[8,9]; therefore, this combination has been selected as an appropriate choice for first-line treatment of locally advanced inoperable and metastatic gastric or GEJ cancer, which is explored in Part B.

The poor prognosis of these cancer types warrants exploration of additional treatment options. One such option is that of targeted therapies, including ADCs. The covalent linking of a cytotoxic "payload", such as DNA-damaging agents or tubulin polymerization inhibitors, to an antibody to form an ADC provides a mechanism for selective delivery of the cytotoxic agent to cancer cells via the specific binding of the antibody to cancer-selective cell surface molecules. ADC strategies do not only enhance the therapeutic window of potent cytotoxic drugs, but also minimize chemotherapy-associated side effects. Antibodies, payloads, and cleavable or non-cleavable linkers can be combined so that the resulting ADCs have various characteristics.[10]

The US Food and Drug Administration's approval of brentuximab vedotin (Adcetris®) in 2011[11] has validated the ADC concept in cancer treatment and stimulated intensive research which led to regulatory approvals of ADCs now used in clinical practice.[12-20]

The claudin multigene family encodes proteins with four membrane-spanning domains that are crucial structural and functional components of tight junctions. In mammals, there are at least 27 claudin members identified and they exhibit complex tissue-specific patterns of expression.[21] CLDN18.2 is highly expressed in the normal stomach, is strictly confined to short-lived gastric epithelial cells, and is absent from the vast majority of healthy tissues. Furthermore, CLDN18.2 is expressed in a significant proportion of primary gastric cancers (up to 96%), GEJ cancers (up to 78%), and ductal pancreatic cancers (up to 80%) and their metastases.[22]

The strong antitumor activity of SOT102 was demonstrated *in vivo* in several relevant mouse models, engrafted with patient-derived gastric, pancreatic, colon, lung, and liver tumors. Importantly, SOT102 was active *in vivo* against tumors expressing CLDN18.2 at high, intermediate, and low levels. The beneficial effect of SOT102 treatment supports the clinical evaluation of this treatment approach. For more detailed information please see the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

Based on preclinical toxicology and efficacy studies, it is assumed that the clinical benefits of SOT102 will outweigh the potential risks. More detailed information about the known and anticipated benefits and risks and potential AEs that could be associated with the administration of SOT102 may be found in the IB. The original intention of the trial was to investigate its objectives in two indications - gastric/GEJ cancer and pancreatic cancer. Following a reassessment of the benefit/risk ratio, it was decided by the sponsor to halt the clinical development in gastric/GEJ cancer for the time being and proceed only with pancreatic cancer. For more details see the IB.

3 OBJECTIVES AND ENDPOINTS

Table 3.1: Part A (SOT102, monotherapy, dose escalation)

Objective	Endpoint
Primary	
• To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of SOT102 given as monotherapy.	• MTD is defined as the highest dose level tested below the dose level associated with ≥33% of dose-limiting toxicity (DLT)-evaluable patients experiencing DLT. The RP2D will be selected based on integrated evaluation of the totality of clinical and preclinical data, for all dose levels tested.
Secondary	
• To assess the safety and tolerability of SOT102 in monotherapy.	• The occurrence of DLTs, occurrence of treatment-emergent AEs (TEAEs), SOT102-related AEs, serious AEs (SAEs), AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities
• To characterize the pharmacokinetics (PK) of total SOT102, conjugated SOT102, [redacted]	• PK of total SOT102, conjugated SOT102, [redacted]
• To explore evidence of SOT102 activity in monotherapy in individual patients.	• Anecdotal tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[23] by type and CLDN18.2 expression
• To explore whether patients develop any antibodies against SOT102.	• The number of patients with detected antibodies against any part of SOT102

Table 3.2: Part B (SOT102 combined with first-line SoC treatment, dose escalation)

Objective	Endpoint
Primary	
• To determine the MTD and RP2D of SOT102 in combination with first-line SoC treatment.	• MTD is defined as the highest dose level tested below the dose level associated with ≥33% of DLT-evaluable patients experiencing DLT. The RP2D will be selected based on integrated evaluation of the totality of clinical and preclinical data, for all dose levels tested.

Objective	Endpoint
Secondary	
• To assess the safety and tolerability of SOT102 in combination with first-line SoC treatment.	• The occurrence of DLTs, occurrence of TEAEs, SOT102-related AEs, SAEs, AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities
• To characterize the PK of total SOT102, conjugated SOT102, [redacted]	• PK of total SOT102, conjugated SOT102, [redacted]
• To explore evidence of SOT102 activity in combination with first-line SoC treatment in individual patients.	• Anecdotal tumor response per RECIST 1.1 by type and CLDN18.2 expression
• To explore whether patients develop any antibodies against SOT102.	• The number of patients with detected antibodies against any part of SOT102

Table 3.3: Part C (SOT102 monotherapy, cohort expansion)

Objective	Endpoint
Primary	
• To assess the efficacy of SOT102 in monotherapy.	• Objective response rate (ORR)
Secondary	
• To evaluate additional measures of efficacy of SOT102 in monotherapy.	• Duration of response (DoR), progression-free survival (PFS) and clinical benefit rate per RECIST 1.1, overall survival (OS)
• To assess the safety and tolerability of SOT102 in monotherapy.	• The occurrence of TEAEs, SOT102-related AEs, SAEs, AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities
• To assess quality of life (QoL) after treatment with SOT102 in monotherapy.	• Assessment of global and disease-specific QoL by patient-reported questionnaires EORTC QLQ-C30 and EORTC QLQ-PAN26 for patients with pancreatic cancer
• To characterize the PK of total SOT102, conjugated SOT102, [redacted]	• PK of total SOT102, conjugated SOT102, [redacted]
• To explore whether patients develop any antibodies against SOT102.	• The number of patients with detected antibodies against any part of SOT102

Objective	Endpoint
Exploratory	
• To assess the relationship between the intensity of CLDN18.2 expression and clinical outcome	• Relationship between the intensity of CLDN18.2 expression and clinical outcome

Table 3.4: Part D (SOT102 combined with first-line SoC treatment, cohort expansion)

Objective	Endpoint
Primary	
• To assess the efficacy of SOT102 in combination with first-line SoC treatment.	• ORR
Secondary	
• To evaluate additional measures of efficacy of SOT102 in combination with first-line SoC treatment.	• DoR and PFS per RECIST 1.1, OS
• To assess the safety and tolerability of SOT102 in combination with first-line SoC treatment.	• The occurrence of TEAEs, SOT102-related AEs, SAEs, AEs leading to premature discontinuation of SOT102, deaths, or clinical laboratory test abnormalities
• To assess QoL after treatment with SOT102 in combination with SoC treatment.	• Assessment of global and disease-specific QoL by patient-reported questionnaires EORTC QLQ-C30 and EORTC QLQ-PAN26 for patients with pancreatic cancer
• To characterize the PK of total SOT102, conjugated SOT102, [redacted]	• PK of total SOT102, conjugated SOT102, [redacted]
• To explore whether patients develop any antibodies against SOT102	• The number of patients with detected antibodies against any part of SOT102
Exploratory	
• To assess the relationship between the intensity of CLDN18.2 expression and clinical outcome	• Relationship between the intensity of CLDN18.2 expression and clinical outcome

4 TRIAL DESIGN

4.1 Overall design

This trial will assess the MTD and RP2D of SOT102 administered as monotherapy (Part A) and in combination with first-line SoC treatment (nab-paclitaxel/gemcitabine for pancreatic cancer, mFOLFOX6 with nivolumab for gastric/GEJ cancer; Part B) and efficacy of SOT102 administered as monotherapy (Part C) and in combination with first-line SoC treatment (Part D) in patients with inoperable or metastatic pancreatic adenocarcinoma whose tumor expresses CLDN18.2 and in ongoing patients with advanced inoperable or metastatic gastric/GEJ adenocarcinoma, who were enrolled in the trial prior to this Protocol Amendment, and are allowed to continue SoC therapy without SOT102 until criteria for SoC therapy discontinuation are met.

CLDN18.2 positivity is determined by immunohistochemistry (IHC) assay. Pancreatic tumor must have medium to high (2+3+) CLDN18.2 membranous staining on ≥75% of tumor cells by IHC.

The trial has the following parts:

- **Part A: Dose escalation, first in human**, single-agent phase 1 trial of SOT102 in advanced/metastatic gastric/GEJ or CLDN18.2-positive pancreatic cancer patients with unmet medical need. Gastric/GEJ cohort is currently halted, and no new patients will be enrolled (for details see the IB).
- **Part B gastric cohort**: Phase 1b dose escalation combination trial of SOT102 in combination with mFOLFOX6 and nivolumab as SoC regimen for first-line treatment of patients with advanced/metastatic gastric/GEJ cancer which that started once monotherapy SOT102 dose level 3 in Part A was successfully completed and was safe; the starting dose of Part B was dose level 1 of Part A. This part is currently halted, and no new patients will be enrolled (for details see the IB).

  Part B pancreatic cohort: Phase 1b dose escalation combination trial of SOT102 in combination with nab-paclitaxel/gemcitabine as SoC regimen for first-line treatment of CLDN18.2-positive patients with advanced/metastatic pancreatic cancer which will start once monotherapy SOT102 dose level 3 in Part A is successfully completed and is safe; the starting dose of Part B will be dose level 1 of Part A

Once an RP2D in the respective phase 1 evaluation (Part A and Part B) has been identified, expansion cohorts for pancreatic cancer (Part C and Part D) are planned:

- **Part C**: Single-agent SOT102 expansion at RP2D identified in Part A in CLDN18.2-positive pancreatic cancer after one or more prior systemic therapies (second+ line) for locally advanced or metastatic disease

  Part D: SOT102 in combination with nab-paclitaxel/gemcitabine for first-line treatment expansion at RP2D identified in Part B in CLDN18.2-positive pancreatic cancer

4.1.1 Dose escalation plan (Part A and Part B)

The DLT evaluation period is 28 days counted from day 1 of cycle 1 of SOT102.

A patient evaluable for DLT will be a patient who has received 2 doses of SOT102 per schedule (day 1 of cycle 1 and day 1 of cycle 2) with the maximum postponement of cycle 2 by 1 day

(as agreed by the sponsor) and who completed the evaluation period of 28 days. Patients who do not fulfill these criteria for any reason other than DLT will be replaced.

In addition to above-mentioned requirements for SOT102 monotherapy, a DLT-evaluable patient in Part B must also meet the following requirements regarding SoC treatment:

- Pancreatic patient who has received three doses of SoC (days 1, 8, and 15 of cycle 1)

After completion of the DLT evaluation period with the adequate number of evaluable patients, all data as specified in a Dose Escalation Committee (DEC) Charter will be reviewed during a Dose Escalation Meeting (DEM) by the DEC. The decision as to whether an AE should be considered as DLT and/or whether a dose level is to be considered intolerable will be made by the DEC. The DEC membership is defined in the DEC Charter.

In the event of a confirmed non-tolerable dose at any dose level, the sponsor will inform all sites immediately. Patients who will not be DLT-evaluable will be replaced. Replaced patients can continue with trial treatment if there is clinical benefit and upon consent with the sponsor.

The dose escalation plan will follow a 3+3 design as described by Hanauske and von Hoff[24] and will include a safety observation period.

If one of the first three patients of a dose level experiences DLT, three more patients will be treated at the same dose level.

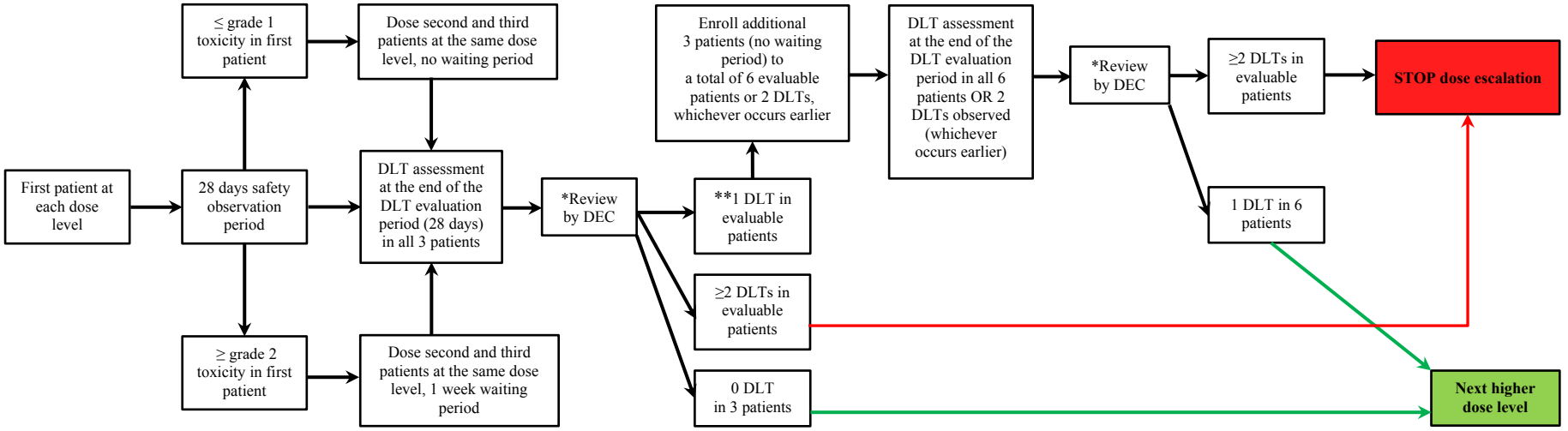
The dose escalation continues until DLTs are observed in ≥2 DLT-evaluable patients at a given dose level. The MTD will be declared as the highest dose level tested below that particular dose level. At least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion parts C and D are initiated.

Staggered enrollment of patients:

For each dose level, the first patient will be observed for safety starting from day 1 of cycle 1 (see section 8.2.3.1). If there are no safety concerns after 28 days, the responsible investigator will notify the sponsor's medical monitor and the second and third patients will be allowed to be dosed according to the following: if the first patient experiences ≤ grade 1 toxicity, the two subsequent patients can be dosed. If the first patient experiences ≥ grade 2 toxicity, each of the two subsequent patients will have an observational period of one week before the next patient can be dosed.

For more details see Figure 4.1.

Figure 4.1: Dose escalation flowchart for Part A and Part B (staggered dosing and 3+3 design)



* The DEC will review, discuss, and decide on the next steps of the trial.

** In the case of 1 DLT only, additional patients may be enrolled without a formal DEC meeting (notification to DEC about the additional enrollment is sufficient)

DEC, Dose Escalation Committee; DLT, dose-limiting toxicity

4.1.1.1 Dose-limiting toxicities definitions

DLTs will be AEs as specified below and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. The AEs listed below will be considered DLTs unless clearly not related to SOT102 (e.g., events clearly due to cancer disease, other comorbid illness, or unequivocally related to concomitant medications or SoC treatment in Part B). The DLT evaluation period is 28 days counted from day 1 of cycle 1. Every DLT in the trial will be discussed between the trial investigators and sponsor and every effort will be made to ensure all clinical assessments are carried out and documented appropriately.

AEs that are considered DLTs:

- All grade 5 events not clearly related to disease progression, or any other causes will be considered DLTs.
- Any grade 3 or higher non-hematologic toxicity regardless of duration will be considered a DLT. The exceptions below are NOT considered DLTs:
  - Grade 3 nausea, vomiting, or diarrhea that can be controlled within 72 hours
  - Grade 3 fatigue less than 5 days
  - Grade 3 or higher correctable electrolyte abnormalities that last less than 72 hours and not associated with clinical complications
  - Grade 3 or higher amylase or lipase not associated with symptoms, or clinical manifestations, or radiological evidence of pancreatitis
- Grade 2 or higher serum creatinine elevation
- Hy's law cases will be considered DLTs (see section 10.2)
- Hematologic DLTs will include the following:
  - Grade 4 neutropenia lasting more than 7 days
  - Febrile neutropenia
  - Grade 3 thrombocytopenia with bleeding
  - Grade 4 thrombocytopenia
- Any grade 2 pneumonitis that does not resolve to grade 1 within 3 days of the initiation of maximal supportive care
- Recurrent grade 2 pneumonitis
- Grade 2 or higher proteinuria

Other clinically significant toxicities, including a single event or multiple occurrences of the same event, may be considered as DLTs.

AEs occurring after the DLT evaluation period may be considered DLT-like events upon DEC discussion. If required, a DEM will be set up to assess these events.

Patients who develop toxicities qualified as DLTs will be discontinued from therapy, unless the investigator determines that the patient has a clear and demonstrable clinical benefit from treatment at the same time.

4.1.1.2 Maximum tolerated dose and selection of the recommended phase 2 dose

If the MTD is reached, the RP2D will be defined based on all available clinical and preclinical information. At least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion parts C and D are initiated.

4.1.1.3 Dose escalation meetings

A DEM will regularly take place after the last patient of the dose level has completed the DLT evaluation period (28 days counted from day 1 of cycle 1) with or without DLTs and is evaluable for DLT assessment. In case of unforeseen severe toxicities, a DEM can be called at any time.

The decision as to whether AEs should be considered as DLTs and/or whether a dose level is to be considered intolerable will be made by the DEC. In the event of a confirmed non-tolerable dose at any dose level, the sponsor will inform all sites immediately.

At every DEM, the totality of clinical and preclinical data will be reviewed by the DEC and will be taken into consideration by the DEM panel.

4.1.1.4 Safety monitoring

4.1.1.4.1 Part A

Patients will be monitored for all AEs which might be associated with SOT102 administration for 30 days after the last dose of SOT102 and for AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment until disease progression or start of new anticancer therapy. These AEs will be monitored every 6 weeks (±2 weeks) during the follow-up period (see section 4.1.2.4). Any late toxicities will be considered in the determination of the MTD/RP2D and dose schedules for Part A.

4.1.1.4.2 Part B

Patients will be monitored at the same visits and with assessments as specified in Part A (for 30 days after the last dose of SOT102 and every 6 weeks [±2 weeks] until disease progression or start of new anticancer therapy) during the combination treatment with SOT102 (see section 4.1.3.4). Any late toxicities will be considered in the determination of the MTD/RP2D and dose schedules for Part B.

The following immune-related reactions were reported in patients treated with nivolumab: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and other immune-mediated adverse reactions (including myocarditis, pericarditis, vasculitis, uveitis, iritis, and other ocular inflammatory toxicities, pancreatitis, myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatic, hypoparathyroidism, hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis [Kikuchi lymphadenitis], sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection).[9,25] All immune-related reactions should be managed according to local standards.

No immune-related reactions were reported in patients treated with nab-paclitaxel/gemcitabine.[26,27]

The following immune-related reactions were reported in patients treated with mFOLFOX6: allergic reactions/allergy (including anaphylactoid/anaphylactic reactions and urticaria); hypersensitivity reactions; bronchospasm, immunosuppression with an increased risk of infection.[28-30] All immune-related reactions should be managed according to local standards.

4.1.1.5 Patient recruitment management

The trial will recruit patients to all ongoing trial parts in parallel.

The sponsor will allocate slots for the patients to be recruited to the dose-escalation trial parts. Potentially eligible patients will be communicated to the sponsor (on an ad-hoc basis and/or at regular meetings) and will be assessed for enrollment with the aim of recruiting patients to a specific dose level as quickly as the rules set out in the dose escalation flowchart allow (Figure 4.1). Available slots will be distributed by the sponsor upon discussion with specific sites to ensure appropriate distribution of patients (e.g., regionally). Back-up slots for screen failure patients or potential failure to manage the DLT evaluation period will also be secured in advance, if possible.

4.1.1.6 Communication plan

Trial investigators will inform the sponsor's medical monitor via an immediate phone call in case of an urgent safety signal, including but not limited to DLTs, life-threatening immune reactions, unexpected event likely to seriously affect the benefit-risk balance of SOT102, and serious safety-related Protocol deviations. The sponsor's medical monitor will ensure all sites are informed immediately, and any preventive measure is put in place, including stopping recruitment temporarily, if required. In case of a DLT, this immediate phone call will be followed by submission of required information within 24 hours via an electronic case report form (eCRF) or via email. The sponsor's medical monitor will immediately inform all sites and a DEM may be arranged. The DEM will assess whether the type and extent of toxicities observed warrants informing all patients enrolled in the trial and will work with investigators to share findings as appropriate.

Regular trial teleconferences will be held between trial investigators (or designated sub-investigators) and the sponsor's medical monitor. In addition to a review of potential patients for recruitment and updates on the status of ongoing patients, any emerging safety issues will be discussed. At these regular teleconferences, the trial investigator or designated sub-investigator will also inform the sponsor's medical monitor of any important toxicities or DLT-like events occurring in the subsequent cycles, i.e., beyond the DLT evaluation period. This will allow appropriate actions to be taken.

Ad-hoc meetings with the trial investigators or designees may also be arranged to discuss any safety concerns during the trial.

4.1.2 Part A (SOT102 monotherapy, dose escalation)

In Part A, patients with CLDN18.2-positive pancreatic adenocarcinoma will be treated with escalating doses of SOT102 given once every 14 days via the intravenous (IV) route over 45 (±15) minutes. If medically indicated, an extension of the infusion time up to 120 minutes is allowed. In this case, the sponsor must be informed. However, a total duration of 120 minutes should not be exceeded.

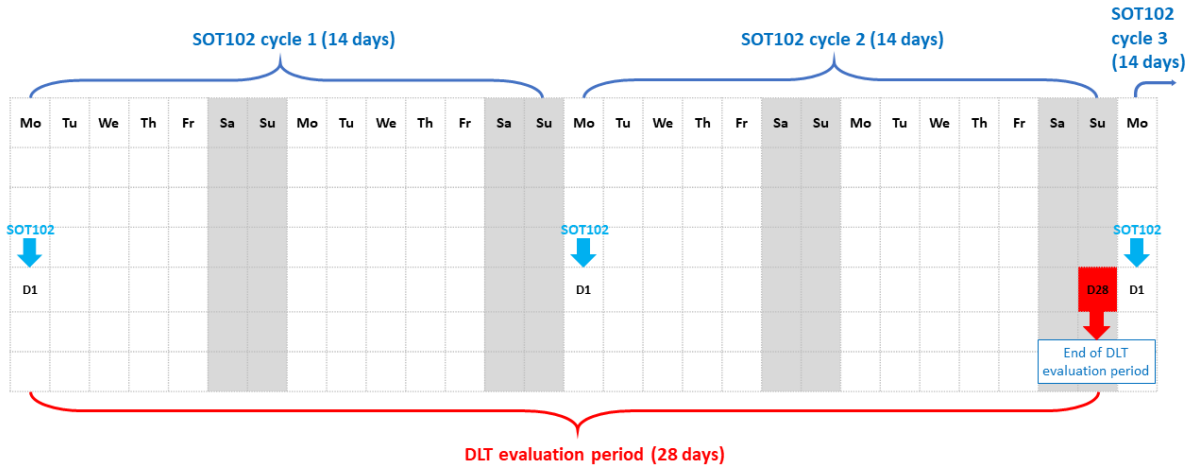
A starting dose of 0.032 mg/kg was selected in Part A of this trial. If only grade ≤1 therapy-related toxicities are observed during cycle 1 in the first three patients at a given dose level, the

dose will be increased by 100% for the next dose level. If grade ≥2 therapy-related toxicities are observed during cycle 1 in any patient at a particular dose level, the dose will be increased by de-escalating dose increases following a modified Fibonacci scheme. These adjustments of the planned dose levels and dose increments will be considered by the DEC.

SOT102 monotherapy dose escalation will continue until DLTs are observed in ≥2 DLT-evaluable patients at a given dose level. The MTD will be declared as the highest dose level tested below that particular dose level. Based on the MTD assessment results, additional doses and schedules may be opened as required to define the dose and schedule of the RP2D.

Please also see Figure 4.2.

Figure 4.2: Part A: SOT102 dosing schedule



Patients with gastric/GEJ cancer were treated according to the same dosing schedule. No patients with gastric/GEJ cancer will be enrolled in the current amended trial (for details see the IB).

4.1.2.1 Screening period

Patients will be screened within a period of not more than 21 days, which will start when the informed consent form (ICF) has been signed and end on the day before day 1 of cycle 1. All Protocol-required screening laboratory tests must be done within 7 days before day 1 of cycle 1. Patients may be rescreened once. Rescreening is subject to the same requirements as screening, including a new ICF signature.

A sample of tumor tissue is required during screening for confirmation of CLDN18.2 expression and measurement of CLDN18.2 levels (per immunohistochemistry [IHC]).

4.1.2.2 DLT evaluation period

The DLT evaluation period will be 28 days starting from day 1 of cycle 1 of SOT102 treatment.

4.1.2.3 Continued treatment period

During the treatment period, the trial assessments will be performed as outlined in the Schedule of activities. Trial interventions will be administered as described in section 6.

Patients without DLT during the DLT evaluation period will continue treatment with SOT102 monotherapy until any of the criteria for treatment discontinuation are met (see section 7.1).

4.1.2.4 Follow-up period

Every effort should be made to monitor all AEs and concomitant medications for 30 days after the final dose of SOT102; whenever possible, all patients will come to the clinic 30 (+5) days after the final dose of SOT102.

Trial participation of patients who discontinue SOT102 therapy after progression of the disease will end by the Follow-up visit 30 (+5) days after the final dose of SOT102.

Patients who discontinue SOT102 therapy prior to progression of the disease will continue to have regular efficacy (tumor) assessments until disease progression or until the start of a new anticancer therapy unless patients withdraw their consent. Trial participation of these patients will end either by the Follow-up visit 30 (+5) days after the final dose of SOT102 or by the last efficacy (tumor) assessment, whichever occurs later.

In addition, the following events must be collected until disease progression or start of new anticancer therapy and monitored via phone calls every 6 weeks (±2 weeks) during the follow-up period:

- AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment (including collection of any concomitant medications)

4.1.3 Part B (SOT102 combined with first-line SoC treatment, dose escalation)

In Part B, patients with CLDN18.2-positive pancreatic adenocarcinoma will be treated with escalating doses of SOT102 given once every 14 days via the IV route over 45 (±15) minutes. If medically indicated, an extension of the infusion time up to 120 minutes is allowed. In this case, the sponsor must be informed. However, a total duration of 120 minutes should not be exceeded. SOT102 will be administered in combination with first-line SoC treatment as follows:

- Nab-paclitaxel (125 mg/m^2) will be given as a 30- to 40-minute infusion followed by gemcitabine (1000 mg/m^2) given as a 30-minute infusion on days 1, 8, and 15. This treatment will be repeated every 28 days.[6]

Hematologic growth factor support is allowed as medically indicated and must be documented.

SOT102 will be administered first and upon completion of the SOT102 infusion, patients will be observed for any acute side effects for 120 minutes. After the observation period, first-line SoC treatment will be administered.

If the SoC treatment needs to be discontinued for medical reasons that do not fulfill the criteria for trial treatment discontinuation, single-agent therapy with SOT102 will continue until any of the trial treatment discontinuation criteria are met (see section 7.1).

Part B will start once monotherapy SOT102 dose level 3 in Part A is successfully completed and is safe. The starting dose of SOT102 in Part B will be Part A dose level 1.

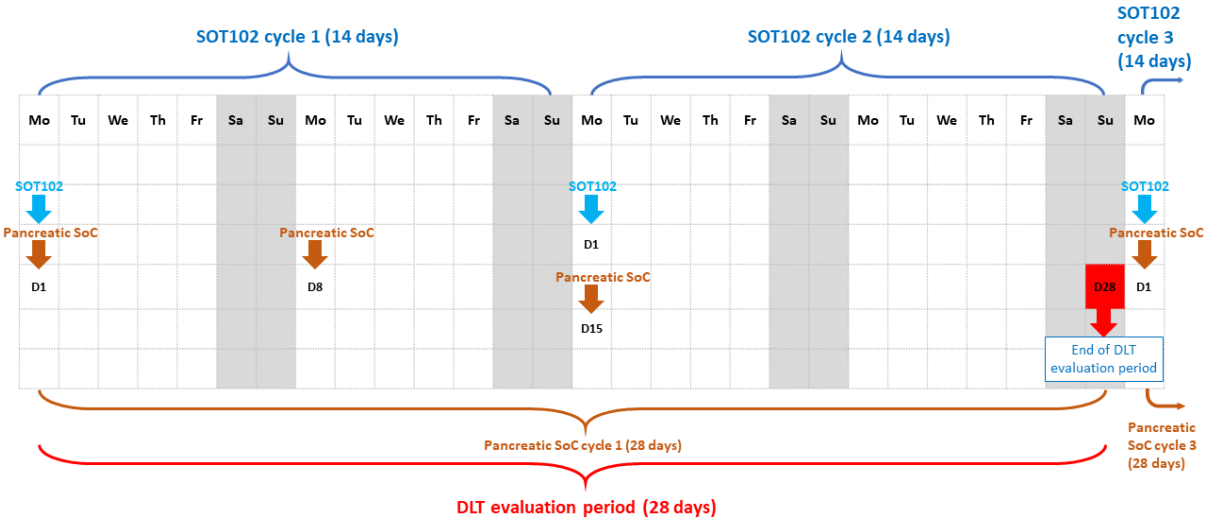
If an MTD in Part A is reached before dose level 3, then the starting dose of SOT102 in Part B will be decided based on review of all available safety/PK data.

The Part B SOT102 dose levels will stay within the safe dose levels of SOT102 monotherapy from Part A. Under no circumstances will the Part B SOT102 dose levels exceed the highest dose deemed safe in Part A.

Dose escalation will follow a modified Fibonacci scheme. Adjustments of the planned dose levels and dose increments will be considered by the DEC.

SOT102 dose escalation in combination with first-line SoC treatment will continue until DLTs are observed in ≥2 DLT-evaluable patients at a given dose level. The MTD will be declared as the dose level below that particular dose level. Based on the MTD assessment results, additional doses and schedules may be opened as required to define the dose and schedule of the RP2D. Please also see Figure 4.4.

Figure 4.4: Part B pancreatic: SOT102 and first-line SoC treatment dosing schedule



Patients with gastric/GEJ cancer were treated according to the same dosing schedule, with the SoC as follows:

- Nivolumab[8] (240 mg) will be given as a 30-minute infusion followed by oxaliplatin (85 mg/m^2) given as a 2-hour infusion and leucovorin (400 mg/m^2) given as a 30-minute infusion, followed by a 5-FU bolus of 400 mg/m^2 followed by 2400 mg/m^2 5-FU given as a 46-hour continuous infusion (mFOLFOX6).[7] This treatment will be repeated every 14 days.

No patients with gastric/GEJ cancer will be enrolled in the current amended trial (for details see the IB).

4.1.3.1 Screening period

Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end on the day before day 1 of cycle 1. All Protocol-required screening laboratory tests must be done within 7 days before day 1 of cycle 1. Patients may be rescreened once. Rescreening is subject to the same requirements as screening, including a new ICF signature.

A sample of tumor tissue is required during screening for confirmation of CLDN18.2 expression and measurement of CLDN18.2 levels (per IHC).

4.1.3.2 DLT evaluation period

The DLT evaluation period will be 28 days starting from day 1 of cycle 1 of SOT102 treatment.

4.1.3.3 Continued treatment period

During the treatment period, the trial assessments will be performed as outlined in the Schedule of activities. Trial interventions will be administered as described in section 6.

Patients without DLT during the DLT evaluation period will continue treatment with SOT102 together with first-line SoC until any of the criteria for treatment discontinuation are met (see section 7.1).

In case SOT102 needs to be discontinued for reasons other than disease progression, first-line SoC treatment will continue until any of the criteria for treatment discontinuation are met. If first-line SoC treatment needs to be discontinued for reasons other than disease progression, SOT102 treatment will continue until any of the criteria for treatment discontinuation are met (see section 7.1).

4.1.3.4 Follow-up period

Every effort should be made to monitor all AEs and concomitant medications for 30 days after the final dose of SOT102; whenever possible, all patients will come to the clinic 30 (+5) days after the final dose of SOT102.

Trial participation of patients who discontinue SOT102 therapy after progression of the disease will end by the Follow-up visit 30 (+5) days after the final dose of SOT102.

Patients who discontinue SOT102 therapy prior to progression of the disease will continue to have regular efficacy (tumor) assessments until disease progression or until the start of a new anticancer therapy unless patients withdraw their consent. Trial participation of these patients will end either by the Follow-up visit 30 (+5) days after the final dose of SOT102 or by the last efficacy (tumor) assessment, whichever occurs later.

In addition, the following events must be collected until disease progression or start of new anticancer therapy and monitored via phone calls every 6 weeks (±2 weeks) during the follow-up period:

- AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment (including collection of any concomitant medications)

4.1.4 Part C (SOT102 monotherapy, cohort expansion)

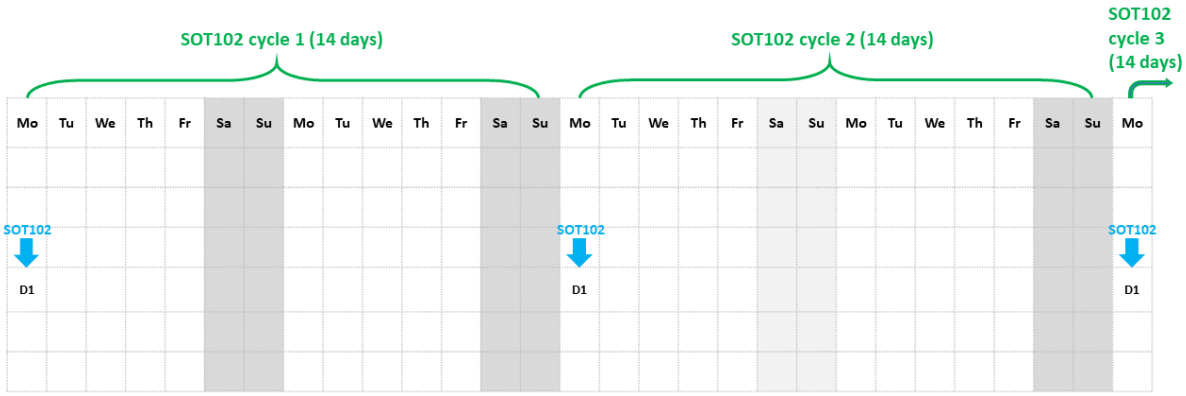
Part C will commence once Part A has established an RP2D. Part C will be performed in patients with CLDN18.2-positive tumors:

- Patients with CLDN18.2-positive pancreatic adenocarcinoma who have received at least one prior line of systemic therapy

Patients will be treated with SOT102 monotherapy at the RP2D identified in Part A given once every 14 days via the IV route over 45 (±15) minutes. If medically indicated, an extension of the infusion time up to 120 minutes is allowed. In this case, the sponsor must be informed. However, a total duration of 120 minutes should not be exceeded.

Please also see Figure 4.5.

Figure 4.5: Part C: SOT102 dosing schedule



4.1.4.1 Screening period

Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end at the time the patient is deemed eligible and enrolled. All Protocol-required screening laboratory tests must be done within 7 days before enrollment. Patients may be rescreened once. Rescreening is subject to the same requirements as screening, including a new ICF signature.

A sample of tumor tissue is required during screening for confirmation of CLDN18.2 expression and measurement of CLDN18.2 levels (per IHC).

4.1.4.2 Treatment period

During the treatment period, the trial assessments will be performed as outlined in the Schedule of activities. Trial interventions will be administered as described in section 6.

Trial treatment should be initiated as soon as possible after the patient is deemed eligible and enrolled in the trial, but no later than 7 days after the enrollment. Patients will be treated with SOT102 until any of the criteria for treatment discontinuation are met (see section 7.1).

4.1.4.3 Follow-up

Every effort should be made to monitor all AEs and concomitant medications for 30 days after the final dose of SOT102; whenever possible, all patients will come to the clinic 30 (+5) days after the final dose of SOT102.

Patients who discontinue SOT102 therapy prior to progression of the disease will continue to have regular efficacy (tumor) assessments until disease progression or until the start of a new anticancer therapy unless patients withdraw their consent.

Patients will be followed up for survival every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until the end of the trial.

4.1.5 Part D (SOT102 combined with first-line SoC treatment, cohort expansion)

Part D will commence once Part B has established an RP2D. Part D will be performed in patients with CLDN18.2-positive tumors:

- Patients with CLDN18.2-positive pancreatic adenocarcinoma

Patients will be treated with SOT102 at the RP2D identified in Part B given once every 14 days via the IV route over 45 (±15) minutes. If medically indicated, an extension of the infusion

time up to 120 minutes is allowed. In this case, the sponsor must be informed. However, a total duration of 120 minutes should not be exceeded. SOT102 will be administered in combination with first-line SoC treatment as follows:

- Nab-paclitaxel (125 mg/m^2) will be given as a 30- to 40-minute infusion followed by gemcitabine (1000 mg/m^2) given as a 30-minute infusion; on days 1, 8, and 15. This treatment will be repeated every 28 days.

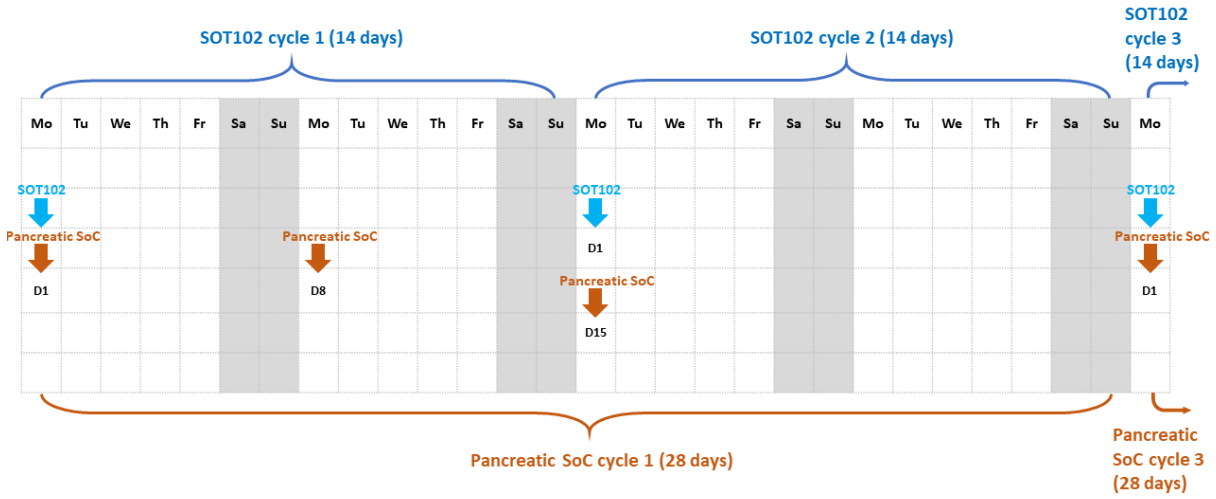
Hematologic growth factor support is allowed as medically indicated and must be documented.

SOT102 will be administered first and upon completion of the SOT102 infusion, first-line SoC treatment will be administered.

If the SoC treatment needs to be discontinued for medical reasons that do not fulfill the criteria for trial treatment discontinuation, single-agent therapy with SOT102 will continue until any of the trial treatment discontinuation criteria are met (see section 7.1).

Please also see Figure 4.7.

Figure 4.7: Part D pancreatic: SOT102 and first-line SoC treatment dosing schedule



4.1.5.1 Screening period

Patients will be screened within a period of not more than 21 days, which will start when the ICF has been signed and end at the time the patient is deemed eligible and enrolled. All Protocol-required screening laboratory tests must be done within 7 days before enrollment. Patients may be rescreened once. Rescreening is subject to the same requirements as screening, including a new ICF signature.

A sample of tumor tissue is required during screening for confirmation of CLDN18.2 expression and measurement of CLDN18.2 levels (per IHC).

4.1.5.2 Treatment period

During the treatment period, the trial assessments will be performed as outlined in the Schedule of activities. Trial interventions will be administered as described in section 6.

Trial treatment should be initiated as soon as possible once the patient is deemed eligible and enrolled in the trial, but no later than 7 days after the enrollment. Patients will be treated with SOT102 in combination with first-line SoC treatment until any of the criteria for treatment discontinuation are met (see section 7.1).

In case SOT102 needs to be discontinued for reasons other than disease progression, first-line SoC treatment will continue until any of the criteria for treatment discontinuation are met. If first-line SoC treatment needs to be discontinued for reasons other than disease progression, SOT102 treatment will continue until any of the criteria for treatment discontinuation are met (see section 7.1).

4.1.5.3 Follow-up period

Every effort should be made to monitor all AEs and concomitant medications for 30 days after the final dose of SOT102; whenever possible, all patients will come to the clinic 30 (+5) days after the final dose of SOT102.

Patients who discontinue SOT102 therapy prior to progression of the disease will continue to have regular efficacy (tumor) assessments until disease progression or until the start of a new anticancer therapy unless patients withdraw their consent.

Patients will be followed up for survival every 3 months (±2 weeks) during year 1 and then every 6 months (±2 weeks) until the end of the trial.

4.2 Scientific rationale for trial design

Malignant transformation of the gastric/GEJ adenocarcinoma cell results in a disruption of cell polarity, causing CLDN18.2 to become exposed, which then becomes accessible to antibody binding. Moreover, CLDN18.2 is aberrantly expressed in malignancies of several other organs, such as pancreatic cancer. SOTIO hypothesizes that targeting predominantly CLDN18.2-expressing tumor cells will avoid the toxic impact on tissue that lacks CLDN18.2 expression, exhibiting a favorable safety profile of SOT102, coupled with a strong cytotoxic effect of linked payload, leading to eradication of tumor cells and thus effective cancer control. Based on CLDN18.2 prevalence in the literature[4,5,31] and sponsor's internal IHC analysis, pancreatic adenocarcinoma was selected as a tumor type with sufficient likelihood of desired IHC positivity and an unmet clinical need for new treatments.

The modular Protocol allows for development of SOT102 in pancreatic patients in advanced lines of therapy as well as exploring efficacy when combined with existing established first-line SoC therapies. Initiation of the combination dose-finding part at the time of dose level 3 of the SOT102 monotherapy is considered adequate to ensure that patients enrolled in the combination (with SoC) dose-finding part of the trial will not be exposed to unreasonable risk.

The original intention of the trial was to investigate its objectives in two indications - gastric/GEJ cancer and pancreatic cancer. Following a reassessment of the benefit/risk ratio, it was decided by the sponsor to halt clinical development in gastric/GEJ cancer for the time being and proceed only with pancreatic cancer. For more details see the IB.

4.3 Justification for dose

4.3.1 Starting dose and dose escalation steps in Part A

The starting dose of the planned trial is based on 1/10 of the body surface-adjusted severely toxic dose in 10% of the animals (STD_{10}) observed in rats and on 1/6 of the body surface-adjusted highest non-severely toxic dose (HNSTD) observed in cynomolgus monkeys.[32]

Considering current data from the rat and cynomolgus monkey dose range finding and Good Laboratory Practice toxicology studies with dose administrations on days 1, 15, and 29 (every

2 weeks), the STD_{10} in rats and the HNSTD in cynomolgus monkeys were determined to be at 2 mg/kg and 0.6 mg/kg, respectively. The conversion according to body surface (allometric scaling factor of 6.2 for rats and 3.1 for and cynomolgus monkeys) and application of the safety margins (1/10 for rats and 1/6 for cynomolgus monkeys) result in both cases in a human starting dose of 0.032 mg/kg. Based on animal PK, exposure at this starting dose is predicted to be approximately 70 µg*h/ml in patients which is about 20-fold and 58-fold lower as observed at the HNSTD in cynomolgus monkeys and at the STD_{10} in rats, respectively.

Based on *in vivo* mouse efficacy studies, strong antitumor activity was observed in patient-derived xenograft models of both pancreatic and gastric carcinoma at the lowest tested dose of 0.2 mg/kg. Based on the allometric scaling factor of 12 for mouse, the human equivalent would be 0.016 mg/kg and thus about 2-fold lower than the selected human starting dose. A comparison by means of exposure concludes that the exposure in mice was about 2.4-fold higher than the expected human exposure. Based on this, SOTIO expects the human starting dose of 0.032 mg/kg to be sufficiently safe with the potential for pharmacological activity and thus considers the starting dose relevant for the treatment of patients.

The choice of dose escalation steps is justified through careful evaluation of toxicities and tolerability of all prior doses administered and is made after consideration of the totality of data available from both clinical and preclinical research.

4.3.2 Starting dose and dose escalation steps in Part B

Part B of the trial will only be initiated once dose level 3 of Part A has been shown to be safe. The choice of the starting dose of SOT102 for Part B rests on the assumption that the difference of three dose levels between Part A and Part B provides an acceptable safety margin for patients about to receive the combination treatment with SoC.

If an MTD in Part A is reached before dose level 3, then the starting dose of SOT102 in Part B will be decided based on the review of all available safety/PK data.

Dose escalation steps in Part B are justified because SOT102 dose levels will stay within the safe dose levels of monotherapy SOT102 from Part A. Under no circumstances will the Part B SOT102 dose levels exceed the highest dose deemed safe in Part A.

4.4 Trial and site start and closure

The first act of recruitment is the signing of the ICF by the first patient, which will also be the trial start date.

A patient is considered to have completed the trial if s/he has completed all periods of the trial, including follow-up calls.

It is expected that the enrollment duration will be 21 months in Part A, 14 months in Part B, 18 months in Part C, and 18 months in Part D. Patients who will respond to therapy will continue with treatment until any of the criteria for treatment discontinuation are met (see section 7.1). The planned overall trial duration is approximately 6 years. The trial will end when the last patient completes the last visit or procedure, including follow-up calls.

The sponsor reserves the right to terminate the trial for medical reasons or any other reason at any time. If the trial is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, regulatory agencies, and institutional review board (IRB) / independent ethics committee (IEC; in the US) / ethics committee (EC; in the EU), or

equivalent committees (outside the US and EU) of the termination or suspension and the reason(s) for the termination or suspension.

The investigator reserves the right to discontinue the trial should his/her judgment so dictate. If the investigator terminates or suspends the trial without prior agreement with the sponsor, the investigator must inform the institution, and the investigator/institution must promptly inform the sponsor and the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) and provide the sponsor and the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) with a detailed written explanation of the termination or suspension.

5 TRIAL POPULATION

5.1 Inclusion criteria

5.1.1 Inclusion criteria applicable to all trial parts

1. Age ≥18 years
2. Written informed consent given prior to any trial-specific procedures
3. Adequate organ function:
   - 3.1. Hematologic: Absolute neutrophil count ≥1.5×10^9/L, platelets ≥100×10^9/L, hemoglobin ≥9 g/dL
   - 3.2. Hepatic: Bilirubin ≤1.5× upper limits of normal (ULN), ALT and AST ≤2.5×ULN; in case of liver involvement: AST and ALT ≤5×ULN
   - 3.3. Renal: Creatinine clearance ≥60 mL/min calculated by Cockcroft-Gault formula (see section 10.3)
   - 3.4. Prothrombin time/international normalized ratio (INR) ≤1.5×ULN
   - 3.5. Albumin ≥3.0 mg/dL
   - 3.6. Proteinuria <1 g/24 hours
   - 3.7. Serum concentrations of potassium, magnesium, and calcium within normal range
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
5. Estimated life expectancy ≥3 months as per investigator's assessment
6. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and one of the following conditions applies:
   - 6.1. Not a woman of childbearing potential (WOCBP). A WOCBP is defined as fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
   - 6.2. A WOCBP who agrees to use a highly effective contraceptive method during the treatment period and for at least 9 months after the last dose of SOT102 or first-line SoC treatment (whichever occurs later)
     - WOCBP can only be included after a negative serum pregnancy test at screening.
     - Highly effective contraception includes:
       - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
         - Oral

    - Intravaginal
    - Transdermal
  - Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - Vasectomized partner provided the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success
  - Sexual abstinence is defined as refraining from heterosexual intercourse during the entire treatment period and for at least 9 months after the last dose of SOT102 or first-line SoC treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

7. Male patients must agree to use a condom during treatment and for 9 months after SOT102 or first-line SoC treatment discontinuation. Male patients wishing to become a father during or after the trial should consider sperm preservation. WOCBP partner of male participant should use highly effective contraception methods for 9 months after SOT102 or first-line SoC treatment discontinuation.
8. Left ventricular ejection fraction (LVEF) ≥50% as determined by echocardiography or nuclear medicine methodology (multiple gated acquisition scanning [MUGA])
9. QTcF interval <450 msec on screening electrocardiogram (ECG)
10. Patient is, in the judgment of the investigator, an appropriate candidate for experimental therapy
11. Patient agrees not to participate in other interventional clinical trials while enrolled in the present trial (with the exception of survival follow-up period)
12. All previous cancer therapies for locally advanced pancreatic cancer and any agents that have not received regulatory approval for any indication must have been discontinued prior to day 1 of cycle 1 (**Note:** not applicable in France, see section 10.8). Patients must have recovered from the acute effects of therapy and treatment-related toxicities must have reached grade ≤1 (exception: alopecia). Mitomycin-C and nitrosoureas must have been discontinued for ≥42 days.
13. Adequate tumor tissue from biopsy or fine needle aspiration (FNA) (formalin-fixed paraffin-embedded [FFPE] blocks), or unstained slides from archival biopsy available or willingness to undergo a fresh tumor biopsy. Pancreatic tumor must have medium to high (2+3+) CLDN18.2 membranous staining on ≥75% of tumor cells by IHC.

Note: Tumor samples will be sent to a central laboratory for CLDN18.2 expression analysis.

5.1.2 Inclusion criteria specific to Part A

14. Patient has advanced inoperable or metastatic disease
15. Patient has received and/or has been determined to be intolerant of all SoC therapy known to confer clinical benefit
16. Measurable or non-measurable disease according to RECIST 1.1
17. Histological or cytological evidence of adenocarcinoma of the pancreas that is advanced or metastatic

5.1.3 Inclusion criteria specific to Part B

14. Patient has advanced inoperable or metastatic disease
15. Patient must have at least one measurable lesion according to RECIST 1.1
16. Histological or cytological evidence of adenocarcinoma of the pancreas that is advanced or metastatic

5.1.4 Inclusion criteria specific to Part C

13. Patient has advanced inoperable or metastatic disease
14. Measurable disease according to RECIST 1.1. At least one measurable lesion must be outside of an earlier radiation field or must have progressed after radiation therapy.
15. Histological or cytological evidence of adenocarcinoma of the pancreas that is advanced or metastatic
16. Must have received at least one prior systemic therapy for advanced or metastatic disease

5.1.5 Inclusion criteria specific to Part D

14. Patient must have at least one measurable lesion according to RECIST 1.1. At least one measurable lesion must be outside of an earlier radiation field or must have progressed after radiation therapy.
15. Histological or cytological evidence of adenocarcinoma of the pancreas that is advanced inoperable or metastatic

5.2 Exclusion criteria

5.2.1 Exclusion criteria applicable to all trial parts

1. Patient has received radiation therapy ≤14 days before day 1 of cycle 1 or has not recovered to grade ≤1 from treatment-related side effects
2. Patient has been previously treated with the maximum cumulative dose of anthracyclines
3. Severe preexisting medical conditions as per judgment of the investigator (e.g., active gastric or GEJ ulcer with or without bleeding, complete or incomplete gastric outlet syndrome with persistent or repetitive bleeding)
4. History of interstitial pneumonitis or pulmonary fibrosis

5. Symptomatic central nervous system malignancy. Patients with asymptomatic or treated central nervous system metastases may be eligible if they are not treated with corticosteroids or anticonvulsants and the disease is stable for at least 60 days.
6. Patient has peripheral sensory neuropathy grade ≥2
7. Active infection requiring systemic therapy that is not clinically controlled before the signature of the ICF
8. Patients with HIV will be eligible if:
    - $CD4^+$ T-cell ($CD4^+$) counts ≥350 cells/uL
    - they have no history of AIDS-defining opportunistic infections
    - they are not currently on HIV therapy

    Patients with hepatitis B will be eligible if:
    - there is serologic evidence of a resolved prior HBV infection (HBsAg-negative and anti-HBc–positive)

    Patients with hepatitis C will be eligible if:
    - they have completed curative antiviral treatment and have HCV viral load below the limit of quantification
9. Alcohol or drug abuse as determined by the investigator
10. Psychiatric condition or social situation that, in the opinion of the investigator, preclude that the patient is able to comply with trial requirements
11. New York Heart Association class ≥2 heart failure, unstable angina, coronary angioplasty, coronary stenting, coronary artery bypass graft, myocardial infarction, cerebrovascular accident or hypertensive crisis within 6 months prior to day 1 of cycle 1
12. History of major ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, Torsades de Pointes)
13. History or family history of congenital long QT syndrome
14. Bradycardia (<50 beats per minute)
15. Family history of sudden cardiac death before age 50
16. Major surgical intervention ≤28 days prior to ICF signature or incomplete wound healing after surgical intervention
17. Time since last transfusion of RBCs ≤14 days before cycle 1 day 1
18. Hypersensitivity or intolerance to any component of trial intervention
19. Vaccination with a live or live-attenuated vaccine within 30 days prior the first dose of trial interventions; the full series (e.g., both doses of a two-dose vaccination series) should be completed prior to dosing if feasible and if delaying enrollment would not put the study subject at risk

5.2.2 Exclusion criteria specific to Part A

20. Any prior systemic therapy for metastatic cancer other than pancreatic cancer. Exception: stable disease under hormonal treatment for prostate cancer, stable disease under hormonal treatment for breast cancer. Prior therapy with fluoropyrimidine or gemcitabine as radiosensitizer during radiation therapy is allowed if such treatment is completed at least 4 weeks prior to day 1 of cycle 1. Patients must have recovered to grade ≤1 from all side effects (exception: alopecia).

5.2.3 Exclusion criteria specific to Part B

20. Patients have received any systemic therapy for metastatic disease. Neoadjuvant and/or adjuvant therapy for pancreatic cancer is allowed if completed ≥3 months prior to day 1 of cycle 1 AND patients must have recovered to grade ≤1 from all side effects (exception: alopecia). Prior therapy with fluoropyrimidine or gemcitabine as radiosensitizer during radiation therapy is allowed if such treatment is completed at least 4 weeks prior to day 1 of cycle 1. Patients must not have received any prior systemic therapy for metastatic cancer other than pancreatic cancer. Exception: stable disease under hormonal treatment for prostate cancer, stable disease under hormonal treatment for breast cancer.
21. Patients with contraindications to any component of the first-line SoC treatment
22. Patients with clinically active inflammatory bowel disease
23. Patients more clinically suitable (e.g., with BRCA1/2 mutation) to receive treatment with leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) as compared to nab-paclitaxel and gemcitabine according to the investigator's opinion

5.2.4 Exclusion criteria specific to Part C

20. Any prior systemic therapy for cancer other than pancreatic cancer. Exception: stable disease under hormonal treatment for prostate cancer, stable disease under hormonal treatment for breast cancer. Patients must have recovered to grade ≤1 from all side effects (exception: alopecia).

5.2.5 Exclusion criteria specific to Part D

20. Patients have received any systemic therapy for metastatic disease. Neoadjuvant and/or adjuvant systemic therapy for pancreatic cancer respectively is allowed if completed ≥3 months prior to day 1 of cycle 1 AND patients must have recovered to grade ≤1 from all side effects (exception: alopecia). Prior therapy with fluoropyrimidine or gemcitabine as radiosensitizer during radiation therapy is allowed if such treatment is completed at least 4 weeks prior to day 1 of cycle 1. Patients must not have received any prior systemic therapy for metastatic cancer other than pancreatic cancer. Exception: stable disease under hormonal treatment for prostate cancer, stable disease under hormonal treatment for breast cancer.
21. Patients with contraindications to any component of the first-line SoC treatment
22. Patients with clinically active inflammatory bowel disease

24. Patients more clinically suitable (e.g., with BRCA1/2 mutation) to receive treatment with FOLFIRINOX as compared to nab-paclitaxel and gemcitabine according to the investigator's opinion

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

Star fruit and grapefruit juice showed inhibition of cytochrome P3A (CYP3A), St. John's wort showed induction thereof. Therefore, co-administration of SOT102 with these foods should be avoided.

5.3.2 Contraception

SOT102 or any of its components may have adverse effects on a fetus *in utero*. Furthermore, it is not known if SOT102 has transient adverse effects on the composition of sperm.

Patients should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy was to occur during the trial. If there is any concern whether a patient of childbearing potential will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

Please also see section 5.1.

5.3.3 Use in nursing women

It is unknown whether SOT102 or any of its components are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breastfeeding are not eligible for enrollment.

Please also see section 5.1.

5.4 Screen failures

Screen failures are defined as patients who consent to participate in the clinical trial by signed ICF but fail to meet the eligibility criteria and are not subsequently enrolled into the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, and AE/SAE as listed in section 8.3.2. Screening assessments, including laboratory tests, may be repeated, if necessary, provided they are carried out within the timelines defined for the screening period. Patients who fail screening due to any reason may be rescreened once. Patients who are rescreened are required to sign a new ICF.

5.5 Criteria for temporarily delaying enrollment/administration of trial intervention

See section 4.1.1 for information on staggered dosing in Part A and Part B.

If a patient experiences an immediately life-threatening or fatal DLT at any dose level (Part A and Part B) or a life-threatening or fatal SAE considered by the investigator to have a suspected causal relationship to SOT102 (i.e., excluding events unequivocally related to cancer) or if

>30% of the treated patients discontinue because of toxicities considered by the investigator to be related to SOT102, the dosing of all patients in the trial will be temporarily stopped until the independent data monitoring committee (IDMC; or DEC for dose escalation parts only) have reviewed the safety data and determined if it is safe to continue and at which dose.

6 TRIAL INTERVENTIONS AND CONCOMITANT THERAPY

6.1 Trial interventions administered

6.1.1 SOT102 (all trial parts)

SOT102 will be administered IV on day 1 of the 14-day cycle. The IV infusion will take 45 (±15) minutes. If medically indicated, an extension of the infusion time up to 120 minutes is allowed. In this case, the sponsor must be informed. However, a total duration of 120 minutes should not be exceeded. One treatment cycle will be 14 days.

Patients will receive premedication with corticosteroids (4 mg dexamethasone twice daily) the day before, the day of (at least one hour prior), and the day after each SOT102 administration.

SOT102 will be supplied in a vial containing lyophilized powder to be reconstituted in water for injection and later diluted in an infusion bag or perfusor syringe containing saline. Also see section 6.2. SOT102 is to be administered in a hospital setting under supervision of the investigator. An intensive care facility and skilled specialists must be available.

6.1.2 First-line SoC treatment (Part B and Part D)

6.1.2.1 Nab-paclitaxel/gemcitabine

The doses of nab-paclitaxel/gemcitabine will be administered as follows: Nab-paclitaxel (125 mg/m^2) will be given as a 30- to 40-minute infusion followed by gemcitabine (1000 mg/m^2) given as a 30-minute infusion on days 1, 8, and 15. This treatment will be repeated every 28 days. Nab-paclitaxel/gemcitabine treatment will be administered after SOT102 administration on day 1 of each cycle.

Both nab-paclitaxel and gemcitabine are commercially available. Always refer to the current/latest approved package inserts/US prescribing information (for the US) and the Summaries of Product Characteristics (SmPC; for the EU) for comprehensive treatment information including, but not limited to, treatment preparation and administration as well as full pharmacologic and safety information.[26,27]

6.1.2.2 mFOLFOX6 and nivolumab

For patients in Part B gastric/GEJ cohort who are continuing on SoC therapy, the SoC is administered as follows:

The doses of mFOLFOX6 and nivolumab components are administered as follows: Nivolumab (240 mg) is given as a 30-minute infusion followed by oxaliplatin (85 mg/m^2) given as a 2-hour infusion and leucovorin (400 mg/m^2) given as a 30-minute infusion, followed by a 5-FU bolus of 400 mg/m^2 followed by 2400 mg/m^2 5-FU given as a 46-hour continuous infusion (mFOLFOX6). This treatment is repeated every 14 days. mFOLFOX6 and nivolumab treatment is administered after SOT102 administration on day 1 of each cycle.

All products that comprise the mFOLFOX6 and nivolumab regimen are commercially available. Nivolumab is to be used as per the approved label in the respective country. Always refer to the current/latest approved package inserts/US prescribing information (for the US) and the SmPCs (for the EU) for comprehensive treatment information including, but not limited to, treatment preparation and administration as well as full pharmacologic and safety information.[9,25,28-30]

6.1.3 Investigational medical device

A medical device manufactured for the sponsor by Roche Tissue Diagnostics provided for use in this trial is Roche Tissue Diagnostics CLDN18.2 IHC Clinical Trial Assay. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the trial and appropriately managed by the sponsor.

6.2 Preparation, handling, storage, accountability

The Pharmacy Manual contains specific instructions for preparation and administration of the SOT102 dose.

SOT102 will be provided by the sponsor as clinical open-labeled supply, labeled in accordance with text that is fully compliant with each participating country's regulations. The primary and secondary label will be translated into the required language(s) for each of those countries.

SOT102 shall be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that SOT102 is kept within 2-8°C. The investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously using either an in-house validated data acquisition system, a mechanical recording device such as a calibrated chart recorder, or manually, so that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

The investigator or designee must confirm appropriate temperature conditions were maintained during transit for all trial interventions received and any discrepancies are reported and resolved before use of the trial interventions.

Only patients enrolled in the trial may receive trial interventions and only authorized site staff may supply or administer the trial interventions. All trial interventions must be stored in a secure, environmentally controlled, and monitored (manually or automatically) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for trial intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused trial interventions are provided in the Pharmacy Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label trial; the treatment will not be blinded.

6.4 Trial intervention compliance

Treatment for each patient will be recorded in the eCRF during the trial. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the trial.

Medication errors and uses outside what is foreseen in the Protocol, including misuse and abuse of SOT102, must be recorded. An underdose or overdose of SOT102 treatment of 10% over or under the dose as defined in section 4.3 needs to be reported.

6.5 Dose modification

6.5.1 Dose modification and toxicity management for SOT102

No dose reduction or treatment delay of SOT102 will be allowed for any dose levels in Part A and Part B in SOT102 cycles 1 and 2. Under exceptional logistics circumstances, and only following a discussion with the sponsor, a treatment delay of +1 day is allowed in Part A and Part B in SOT102 cycles 1 and 2. In Part A and Part B, starting from cycle 6, SOT102 can be administered on day 1 ±1 day.

In a patient who develops DLT, treatment will be discontinued unless the investigator determines that the patient has a clear and demonstrable clinical benefit from treatment at the same time. Further continuation of therapy in these specific circumstances must be discussed with the sponsor and an adequately customized dose must be agreed upon between the investigator and the sponsor. Treatment delay or reduction is only possible after a discussion with the sponsor.

In case a patient develops a grade ≥3 AE or an intolerable persistent grade 2 AE after the DLT evaluation period in Part A and Part B, the treatment will be delayed. If the AE reverts to grade ≤1 within 4 weeks from the day of the previous dose of SOT102, the treatment may resume, otherwise the treatment needs to be discontinued permanently. In case the patient develops a grade 4 AE, the treatment needs to be discontinued permanently.

In Part C and Part D, in case a patient develops a grade ≥3 AE or an intolerable persistent grade 2 AE anytime during the treatment period, the treatment will be delayed. If the AE reverts to grade ≤1 within 4 weeks from the day of the previous dose of SOT102, the treatment may resume, otherwise the treatment needs to be discontinued permanently.

Once the treatment is resumed, the next dose of this patient will be reduced initially by 25% of the initial dose. If the AE will not resolve or will worsen again, the next dose will be further reduced by 50% of the initial dose. If the AE will still not resolve or will worsen, the treatment needs to be discontinued permanently.

In Part C and Part D, starting from cycle 2, SOT102 may be administered on day 1 ±1 day.

In case a patient develops significant toxicities and at the same time has a demonstrable clinical benefit from treatment, further continuation of therapy must be discussed with the sponsor and an adequately customized dose must be agreed upon between investigator and sponsor. Treatment delay or reduction is only possible after a discussion with the sponsor.

Any treatment-related toxicity will be managed by concomitant medication (as appropriate) or by SoC treatment delay, treatment discontinuation, or a combination of these.

6.5.2 Dose modification and toxicity management for first-line SoC treatment

Treatment modifications of first-line SoC treatment (Part B and Part D) are allowed according to the approved labels or as per local or institutional guidelines.[9,25-30] In Part B, starting from cycle 6, first-line SoC treatment can be administered on day 1 ±1 day. In Part D, starting from cycle 2, first-line SoC treatment can be administered on day 1 ±1 day. In case an AE cannot be clearly attributed to any of the first-line SoC treatment agents, treatment modifications will follow the general principle:

In the occurrence of grade ≥3 AE, both the treatment with SOT102 and the first-line SoC treatment will be delayed, while on the second occurrence of grade ≥3 AE, SOT102 will be discontinued permanently.

If the SoC treatment needs to be discontinued for medical reasons that do not fulfill the criteria for trial treatment discontinuation, single-agent therapy with SOT102 will continue until any of the trial treatment discontinuation criteria are met (see section 7.1).

6.6 Continued access to trial intervention after the end of the trial

No trial intervention is planned to be administered to patients after the end of the trial.

6.7 Treatment of overdose

Side effects following administration of SOT102 during the preclinical studies appeared to be dose related. Exceeding the prescribed dose in the trial may be associated with increased toxicity. Symptoms which persist after stopping the treatment with SOT102 should be closely monitored and treated supportively.

6.8 Concomitant therapy

The investigator should instruct patients to notify the investigational site about any new medications taken since screening. All medications and non-drug therapies (e.g., blood transfusions) administered after screening must be listed in the eCRF.

Concomitant administration of live or live-attenuated vaccines are not allowed within 30 days prior to the first dose of trial interventions, during the trial and within 90 days after the last dose of SOT102 and/or SoC, whichever is later. Note: Inactivated vaccines are allowed.

6.8.1 Rescue medication and supportive care

Supportive care can be provided based on investigator judgment according to local institutional guidelines. For first-line SoC treatment, the approved local labels must be followed.[9,25-30] In principle, only authorized medicinal products should be used as auxiliary medicinal products (AxMP) in clinical trials. In exceptional cases where no authorized AxMP are available in the EU or in other countries, or when it cannot reasonably be expected to use an authorized AxMP for the acute treatment of serious health problems in trial subjects in the context of management of toxicities, non-authorized medicinal products may be used on the basis of clinical management guidelines.

6.8.2 Drug-drug interaction potential

In vitro studies addressing cytochrome P450 (CYP450) activities, and their inhibition identified [redacted] and [redacted]-linker containing metabolites as potential inhibitors of CYP3A4 and CYP2D6, respectively. However, based on the absence or low abundance of these structures in animals and based on the potentially achievable concentrations following SOT102 administration, inhibition of CYP3A4 and CYP2D6 in patients seems unlikely. Please refer to the IB for more details.

6.8.3 Medications requiring special caution

Considering the potential risk, caution should be exercised when administering SOT102 with medications known to inhibit either CYP3A4 or CYP2D6. Caution should be also exercised

when administering SOT102 with medications known as substrates of CYP2D6 and CYP3A. Caution should be also used with medications known to or with the potential to prolong QT/QTc interval. For an overview of some of the medications see section 10.5.

Since [redacted] is a substrate of CYP2C9 as well, use of concomitant medications that are known inhibitors or inducers of CYP3A4 or CYP2C9 should be avoided in Part A and B in order to minimize any effect on exposure to [redacted] or [redacted]-linker-containing metabolites.

Patients in Part C and D receiving SOT102 and comedications that are known inhibitors or inducers of CYP3A4 or CYP2C9 need to be closely monitored for AEs. For an overview of some of the medications see section 10.5.

Given the nephrotoxic properties of NSAIDs or other potentially nephrotoxic medications, these should be used with caution and at the discretion of the investigator during treatment with SOT102.

Caution should be used with the following medications when administering first-line SoC treatment.

6.8.3.1 mFOLFOX6

For patients in Part B gastric/GEJ cohort who are continuing on SoC therapy, concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the trial. Some of the medications that may prolong the QT interval are listed in section 10.5.

Various agents have been reported to biochemically modulate the antitumor efficacy or toxicity of fluorouracil, such as:

- Methotrexate
- Folic acid antagonists (e.g., cotrimoxazole, pyrimethamine)
- Anti-epileptic substances (phenobarbital, primidone, phenytoin and succinimides)
- Purines (inosine, guanosine, guanosine-5'-phosphate and deoxyinosine), pyrimidines (thymidine, uridine and cytidine), and antimetabolites (e.g., hydroxyurea)
- Tamoxifen, interferon, phosphonoacteyl-L-aspartate, allopurinol, dipyridamole
- Warfarin
- Brivudine and sorivudine
- Levamisole
- Phenytoin

6.8.3.2 Nab-paclitaxel

Caution should be exercised when administering medications known to induce or inhibit either cytochrome P2C8 (CYP2C8) or cytochrome P3A/P3A4 (CYP3A/CYP3A4). In the EU (per nab-paclitaxel EU SmPC), CYP2C8 and CYP3A4 inducers are not recommended in cohorts including nab-paclitaxel. Caution should be also used with medications known to or with the potential to prolong QT/QTc interval. For an overview of some of the medications see section 10.5 and also the EU SmPC.[26]

7 DISCONTINUATION OF TRIAL INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial intervention

Patients will be discontinued from trial treatment (SOT102 or SOT102/first-line SoC treatment respectively) for any of the following events:

- Radiographic disease progression per RECIST 1.1
- Clinical disease progression (investigator assessment)
- AE (intercurrent illness or trial treatment-related toxicity) that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of trial treatment
- During the DLT evaluation period, any DLT/DLT-equivalent event
- Following the DLT evaluation period: any DLT-like event, specifically grade 2 or higher serum creatinine elevation, grade 2 or higher proteinuria
- Patient may withdraw from the trial at any time for any reason; the investigator must make reasonable effort to determine the reason for this decision and record it in source documentation of the patient
- Death
- Pregnancy
- Patient non-compliance
- Lost to follow-up
- Trial terminated by the sponsor
- If, in the opinion of the investigator, continuation of treatment is no longer in the best interest of the patient

See also section 5.5.

7.2 Patient discontinuation/withdrawal from the trial

A patient may elect to withdraw from the trial at any time for any reason. All patients who withdraw from the trial are to complete the last Follow-up visit as indicated in the Schedule of activities.

A patient who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

7.3 Lost to follow-up

A patient will be considered lost to follow-up if s/he repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts will be documented in the patient's medical record.
- Should the patient continue to be unreachable, s/he will be considered to have withdrawn from the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Schedule of activities. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial interventions.

Adherence to the trial design requirements, including those specified in the Schedule of activities, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., CT scans) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the Protocol-specified criteria and were performed within the time frame defined in the Schedule of activities.

At screening, demography information will be collected (age at screening, gender, race, and ethnicity). Relevant medical and surgical history must be available and noted in the eCRF. Information on history of current malignancy will be collected, including histology/cytology, initial diagnosis date, details about previous systemic and non-systemic treatment together with the associated disease response and date of last disease progression, and any prior mutations/genetic analysis. Other baseline assessments will be done as defined in the Schedule of activities.

8.1 Efficacy assessments

Tumor assessments will be performed by investigators and assessed per RECIST 1.1 for all tumor indications. Radiology images acquired for tumor assessments will be provided to a dedicated vendor for blinded independent assessment as per RECIST 1.1, for all indications in Part C and Part D.

8.1.1 Radiologic evaluation of disease

Disease response and disease progression will be evaluated in this trial using RECIST 1.1 criteria by contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis and/or magnetic resonance imaging (MRI). Other areas might be assessed during the course of the trial, if clinically indicated (e.g., brain). The imaging method used at baseline should be used throughout the trial unless otherwise medically indicated.

Contrast (IV and oral) enhanced spiral CT is a preferred imaging modality. In case of hypersensitivity to contrast medium, the thoracic CT should be performed without IV contrast medium. In such cases, the abdomen and pelvis should be imaged by MRI, or patients can undergo a desensitization procedure, or be pre-medicated as per local guideline.

CT may be replaced by MRI during the course of the trial for patients with contraindications to the administration of contrast agents, or due to other medical reasons, at the discretion of the investigator.

The first scan after the initiation of trial interventions should be performed at 6 weeks (±2 weeks) from cycle 1 day 1. Subsequent tumor scans should be performed every 6 weeks (±2 weeks) or more frequently if clinically indicated, as per Schedule of activities.

The baseline disease assessment will be performed before the initiation of trial treatment and response assessments will be performed as indicated in the Schedule of activities.

8.1.2 Quality of life assessments (only in Part C and Part D)

To determine the effect of trial intervention on the QoL, patient-reported questionnaires EORTC QLQ-C30 and EORTC QLQ-PAN26 for patients with pancreatic cancer will be utilized for this trial.

A baseline assessment will be done at screening. Patients will complete the questionnaires on day 1 of cycles 1 and 4 and at the Follow-up visit 30 days after the last dose of SOT102, as indicated in the Schedule of activities.

EQ-5D-3L questionnaires will be completed. A baseline assessment will be done at screening, and subsequent assessments will be completed by patients every other SOT102 treatment cycle, until the completion of SOT102 therapy. Afterwards, the frequency will be every 16 weeks during year 1 and then every 6 months until the end of trial.

If feasible, the questionnaires should be completed before trial procedures and/or SOT102 administration.

8.1.3 Survival information assessments (only in Part C and Part D)

Survival information will be collected as indicated in the Schedule of activities.

8.2 Safety assessments

Safety monitoring of the patients during the trial will include assessments, physical examinations, vital signs monitoring, and laboratory tests as described below. In Part A and Part B, the DLT evaluation period is 28 days starting from day 1 of cycle 1 of SOT102 treatment. After that period and in Part C and Part D, the assessments, examinations, and laboratory tests will continue as specified in the Schedule of activities.

If patients feel unwell at any point in time during the trial after being discharged from the hospital, they should contact their trial investigator.

All assessments will be carried out in accordance with standard local institutional practice, unless otherwise stated in the Protocol.

8.2.1 Physical examinations, body height, weight, and surface area, ECOG performance status

General physical examination with organ/system-specific physical examination will be carried out by a licensed physician (or the physician's assistant or a nurse practitioner).

For screening and subsequent visits, a complete physical examination, laboratory tests as well as determination of body height, weight, and surface area will be performed according to the Protocol schedule outlined in the Schedule of activities.

ECOG performance status will be assessed at screening, during the trial, and at the Follow-up visit 30 days after the last dose of SOT102, as indicated in the Schedule of activities.

8.2.2 Vital signs

Vital signs will include body temperature, blood pressure (systolic and diastolic, after ≥15 minutes of rest), and heart rate. See also section 8.2.3.

8.2.3 Special assessments on treatment days

8.2.3.1 Cycle 1 day 1

In cycle 1 of Part A and Part B, patients may be hospitalized for 24 hours after the first dose of SOT102 on day 1, or longer if clinically indicated, and will be closely observed for any AEs. Patients in Part C and Part D may be hospitalized only if clinically indicated.

Vital signs (body temperature, heart rate, and systolic and diastolic blood pressure) will be documented at the following frequency at minimum, unless clinically required otherwise:

- Prior to SOT102 administration
- 15 (±5) minutes after the end of SOT102 infusion
- 60 (±5) minutes after the end of SOT102 infusion

8.2.3.2 Cycle 2 and onwards

For the subsequent cycles in all trial parts, patients may be observed in the hospital following SOT102 administration if clinically indicated.

During post-SOT102 observation, vital signs (body temperature, heart rate, and systolic and diastolic blood pressure) will be documented at the following frequency:

- Prior to each SOT102 administration
- 15 (±5) minutes after the end of SOT102 infusion
- 60 (±5) minutes after the end of SOT102 infusion

8.2.4 Electrocardiography

As outlined in the Schedule of activities, in Part A and Part B, an ECG will be done prior to SOT102 infusion and within 15 minutes after the end of SOT102 infusion in each cycle and as clinically indicated. In cycle 1 and 3 it will be additionally done 24 (±2) hours after the end of SOT102 infusion. The ECG collection plan in Part C and Part D, will be re-evaluated based on the emerging data from Part A and Part B.

In the event of grade ≥3 corrected QT/QTc interval prolongation, close and appropriate ECG monitoring (continuously) in hospital will be conducted until a cardiologist's opinion is issued.

8.2.5 Clinical safety laboratory assessments

The standard clinical laboratory analyses are to be performed by a local laboratory. Results from laboratory analysis performed by a local laboratory will be documented in the eCRF. Results from laboratory analysis performed by a central laboratory will be provided to the sponsor, investigator (where applicable), or a contracted party. Details on the collection, handling, storage, and shipment of samples; and reporting of results by the laboratory/laboratories are provided to the investigator in the Laboratory Manual. More frequent evaluations may be performed at the investigator's discretion if medically indicated; results of these additional tests should be recorded in eCRFs.

The sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for the local laboratory/laboratories. Laboratory values that are out of reference ranges will be evaluated for their clinical significance. Laboratory abnormalities that do not meet the criteria of clinical relevance as judged by the investigator do not need to be reported as AEs.

It should be noted that severity and seriousness are different criteria for the evaluation of AEs (please see more details in section 8.3.1.4). Therefore, grade 3 and grade 4 laboratory events (evaluated per NCI CTCAE [v5.0]) do not automatically classify as SAEs unless they meet seriousness criteria as per definition (see section 8.3.1.2).

The timing of the laboratory tests to be done during the trial is specified in the Schedule of activities. From cycle 2 onwards in all trial parts, safety laboratory tests (as listed in the Schedule of activities) can be performed one day early before SOT102 or first-line SoC treatment scheduled dosing.

An overview of laboratory tests to be performed is presented in section 10.4.

8.2.6 Left ventricular ejection fraction

LVEF will be assessed using either echocardiography or nuclear medicine methodology (MUGA scan) in Part A and Part B at screening, every 2 months during the trial (± 2 weeks), and at the Follow-up visit 30 days after the last dose of SOT102; and in Part C, and Part D at screening and as clinically indicated. However, the method chosen needs to stay the same throughout the trial.

8.2.7 Esophagogastroduodenoscopy

Esophagogastroduodenoscopy will be performed at screening and thereafter if clinically indicated.

8.3 Adverse events, serious adverse events, and other safety reporting

8.3.1 Definitions

8.3.1.1 Adverse events

International Council for Harmonisation (ICH) guideline E2A defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver), symptom (e.g., nausea, chest pain), abnormal result of an investigation (e.g., laboratory finding), or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

According to the US Food and Drug Administration (21CFR312.32), an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

8.3.1.2 Serious adverse events

An SAE is any untoward medical occurrence that at any dose fulfills one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is another medically significant event defined as an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent any of the above listed outcomes

8.3.1.3 Excluded events

Hospitalization for the following reasons will not be regarded as serious (not immediately reportable):

- Routine treatment or monitoring of the disease under study, including hospitalization due to trial-related procedures, not associated with any deterioration of the patient's status
- Elective or pre-planned treatment (before signing the ICF) for a preexisting condition that is unrelated to the disease under study and has not worsened since signing the ICF
- Social reasons, respite care, and in the absence of a medical condition (e.g., for observational purposes without any intervention)

8.3.1.4 Severity/intensity vs. seriousness

ICH E2A: The term "severe" is often used to describe the intensity (severity) of a specific event (as mild, moderate, or severe myocardial infarction); the event itself, however, may be of a relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3.2 Time period and frequency for collecting AE, SAE, and other reportable safety event information

Every effort should be made to collect all AEs (as listed below) from the date of the patient's signing the ICF until 30 days after the final administration of SOT102:

- (S)AEs regardless of their causal relationship to SOT102

In addition, the following events must be collected in Part A and Part B until disease progression or start of new anticancer therapy during the follow-up period *(i.e., beyond 30 days after the final administration of SOT102)*:

- AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment (including collection of any concomitant medications)

Additionally, any SAE brought to the attention of an investigator **at any time outside of the time period specified above** must be reported immediately to the sponsor if the event is considered as having a suspected causal relationship to SOT102 per the investigator's judgment.

Pregnancies of the patient or patient's female partner must be reported from the date of the patient's signing the ICF up to 9 months after the final administration of SOT102.

8.3.3 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.4 Follow-up of AEs and SAEs

The investigator assesses at each visit (or more frequently, if necessary) if there are any changes in AE diagnosis, severity, suspected causal relationship to clinical trial medication/procedure, interventions required to treat the event, and AE outcome.

AEs are monitored (followed up) until resolution or until 30 days after the last dose of SOT102. All SAEs will be followed until resolution, stabilization (becoming a permanent condition), or the patient is lost to follow-up as defined in section 7.3.

8.3.5 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of an investigational medicinal product under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational medicinal product under clinical investigation. The sponsor or designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU), and investigators.

An investigator who receives a periodic or expedited safety report (e.g., summary or listing of suspected unexpected serious adverse reactions [SUSARs]) or other specific safety information from the sponsor or designee will review and then file it along with the IB and will notify the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU), if appropriate according to local requirements.

The sponsor will also ensure communication of SUSARs in association with SOT102 to all participating investigators in line with the national safety reporting requirements.

Adverse reactions will be reported to the US FDA according to 21CFR312.32.

8.3.6 Pregnancy

Pregnancy is not considered an (S)AE unless it meets any criteria for becoming serious (see the definitions in section 8.3.1.2). However, patients must inform the investigator of any newly identified pregnancy or pregnancy of their partners without delay. If a patient or patient's female partner becomes pregnant while on treatment, the treatment must stop immediately.

Consent to report information on the outcome of the pregnancy of patients or male patients' partners needs to be obtained from the patients or male patient's pregnant partners.

Pregnancies will be monitored by the investigator to determine the outcome, including spontaneous abortion or voluntary termination, birth details, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications. Every infant must be followed up for 2 months after delivery.

Egg and sperm donation is not allowed during the treatment period and for at least 9 months after the last dose of SOT102.

8.3.7 Assessing AEs

Information about adverse reactions (causally related events) known for SOT102 will be found in the IB or will be communicated between IB updates in the form of a "Dear Investigator Letter".

8.3.7.1 Causality

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the trial intervention.

The investigator needs to assess and report the causal relationship of any AE to:

- SOT102
- First-line SoC treatment (Part B and Part D only)
- Other suspected cause(s) of the event (e.g., concurrent disease, concomitant medication, further-line therapy)

This assessment is based on the investigator's clinical judgment, taking into account all relevant information available at the time of AE reporting, including (but not limited to):

- Temporal association of the event onset with administration of the medication/procedure
- Known type of reaction for any of the administered medication
- Disappearance or abating of symptoms when the medication is discontinued, or the dose is reduced
- Reappearance of symptoms when the medication is re-administered
- Event may or may not be caused by the patient's health condition
- Presence of risks or factors not related to trial treatment that are known to be associated with the occurrence of the event

Causal relationship of all AEs will be classified as follows:

- **Not suspected**: It is not plausible that the AE is caused by medication/procedure and a likely alternative explanation exists.

  No reasonable possibility of a causal or temporal relationship.

- **Suspected**: It is plausible that the AE is caused by medication/procedure.

  Reasonable possibility of a causal relationship.

  *For the purposes of safety reporting, **"reasonable possibility"** means there is evidence to suggest a causal relationship between one of the medications/procedures and the AE.*

8.3.7.2 Severity/intensity

Severity or intensity of an AE must be assessed according to the NCI CTCAE, version 5.0.

8.3.8 Reporting by the investigational site

8.3.8.1 Adverse events

Any AE (including SAEs), whether or not considered to be causally related to the trial medication and regardless of its seriousness, must be reported (described and recorded) in the AE section of the patient's eCRF on an ongoing basis.

Only clinically relevant abnormal laboratory values, vital signs, or examination abnormalities need to be documented as AEs. Whenever possible, a diagnosis rather than symptoms should be provided on the AE eCRF page (e.g., anemia instead of low hemoglobin).

Clinically relevant here means: induce clinical signs or symptoms, require therapy (e.g., hematologic abnormality requiring treatment), require a change in trial medication(s), or require a change in the clinical trial schedule or per investigator's discretion.

Physical examination findings will be compared with the baseline status and any significant change, as assessed by the investigator, must be documented as an AE.

A surgical procedure is not an AE but a therapeutic measure for a condition that necessitates surgery. Therefore, the condition for which the surgery is required must be reported as an AE.

Any pre-planned surgery (i.e., planned before signature of the ICF) or other intervention permitted by this trial Protocol and the condition leading to that measure are not AEs. In such cases, the underlying condition needs to be documented in the patient's medical history in the eCRF.

Death itself is not an AE term but the outcome of an event, which needs to be described using medical terminology. Information about death will be captured on the respective eCRF page along with relevant details (date of death, immediate and underlying causes of death).

8.3.8.2 Documenting in eCRFs

The reported term needs to be a medical diagnosis or sign/symptom of the event, not a procedure. Each symptom in a constellation of symptoms should be listed separately if the investigator has not set a diagnosis.

Fluctuations or re-occurrences of a condition, which are considered normal for the patient and are recorded in the patient's eCRF medical history, do not need to be reported as an AE. However, if the condition deteriorates during the trial, it needs to be captured as an AE.

If the same AE occurs repeatedly, it must be assessed and documented separately each time.

If possible, each AE should be evaluated to determine:

- Event term or a description of the AE in medical terms (not as reported by the patient)
- Severity grade or intensity of the event as assessed by the investigator (1-5 according to the NCI CTCAE version 5.0)
- Its causal relationship to SOT102, as assessed by the investigator (suspected; not suspected)
- Its causal relationship to first-line SoC treatment (Part B and Part D only), as assessed by the investigator (suspected; not suspected)
- Event duration, including onset date and end date
- Action taken with SOT102 due to the reported event

- Action taken with first-line SoC treatment due to the reported event
- Event seriousness (non-serious or serious AE)
- Event outcome (resolved, resolved with sequelae, not resolved, resolving, fatal, unknown)

8.3.8.3 Immediately reportable events

The investigator or any investigational site staff must immediately (**within 24 hours of awareness at the latest**) notify/report to the sponsor's designated Pharmacovigilance department any initial or medically relevant follow-up information about these events:

- SAE
- Pregnancy of the patient or patient's female partner

The initial notification can be made via email. This notification must be followed within an additional 24 hours by a written report (i.e., a completed SAE Report Form or Pregnancy Data Collection Form), providing all available information and a detailed narrative description. A formless notification (without a report form) is not required if the initial/follow-up information is reported on the appropriate form within 24 hours of knowledge.

The investigator must not wait to receive additional information to fully document the event before notifying the sponsor's designated Pharmacovigilance department **primarily via the eCRF system**; or via:

Email: [redacted]

Follow-up information must be sent within the same timelines using the same contact details as outlined above.

Additionally, refer to the Safety Reporting Instructions for Sites for information on how to report these events.

Minimum notification/reporting requirements

The following information must be provided for a valid notification/report:

1. Identification of the notifying/reporting person (e.g., name of the reporter)
2. Identification of the patient (e.g., patient number)
3. Concerned trial treatment (SOT102) or clinical trial (e.g., SN201, CLAUDIO-01)
4. Reason for notification/reporting (i.e., SAE, pregnancy of the patient or patient's female partner)
5. Event term

*In addition, providing an **assessment of the causal relationship** is necessary for comprehensive evaluation by the sponsor and potential regulatory submission.*

8.3.8.4 Report forms

The SAE Report Form is **primarily completed within the eCRF system** for the trial and submitted to the sponsor's designated Pharmacovigilance department. In case the eCRF system is not available/accessible, a paper SAE Report Form is filled out and sent to the sponsor's designated Pharmacovigilance department (see details above).

For reporting of pregnancies, the paper Pregnancy Data Collection Form is to be used. Completion guidelines provide information on format and details of the information required.

The originals of the paper report forms must be kept in the site trial file.

The report forms need to be completed in English.

All immediately reportable events from the investigational site to the sponsor's designated Pharmacovigilance department (i.e., SAEs and patients' or partners' pregnancies) must also be recorded in the site's source documentation and in the eCRF as appropriate.

8.4 Pharmacokinetics

Plasma concentrations of SOT102 will be tabulated and summarized by dose level, day, and time.

The following PK parameters will be analyzed for total SOT102, conjugated SOT102, [redacted]

- Maximum concentration observed (C_{max})
- Time of maximum concentration observed (T_{max})
- Area under the curve (AUC)

If possible, also the following will be analyzed:

- Elimination half-life ($t_{1/2}$)
- Total body clearance
- Volume of distribution
- Accumulation ratio

Further details will be specified in the Pharmacokinetic Analysis Plan or similar document as applicable.

The actual date and time (24-hour clock time) of each sample will be recorded.

Instructions on sample collection, handling, storage, and shipment of samples are detailed in the trial-specific Laboratory Manual provided to the trial site.

8.5 Genetics

Not applicable.

8.6 Tumor biopsy

A sample of tumor tissue is required during screening for assessment of CLDN18.2 levels (per IHC) in the tumor. Fresh tissue (in formalin-fixative) or archived formalin-fixed paraffin-embedded (FFPE) tissue/FNA are acceptable. The tumor must be CLDN18.2-positive for the patient to be enrolled in the trial. IHC testing will be performed at a central laboratory. Refer to the Laboratory Manual for further details regarding biopsy collection and shipment.

Note: Given the length of time needed for IHC testing and the approximately 14-36% chance that a pancreatic cancer biopsy will meet the positivity threshold, this activity should be performed at the initiation of the screening period.

8.7 Biomarkers

No other biomarkers than CLDN18.2 will be assessed in this trial.

8.8 Immunogenicity assessments

Samples for anti-drug antibodies (ADAs) will be collected to assess SOT102 tolerance, correlation with PK, and potential AEs associated with ADAs against SOT102 and for the prediction of SOT102 ADA production.

Instructions on sample collection, handling, storage, and shipment of samples are detailed in the trial-specific Laboratory Manual provided to the trial site.

Samples will be stored for a maximum of 15 years (or according to local regulations) after the end of the trial at a facility selected by the sponsor to enable further analysis of immune responses to SOT102.

8.9 Health economics

Health economics parameters will not be evaluated in this trial.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Each trial part will be analyzed separately following its objectives. Each indication (cohort) in Part B, Part C, and Part D will be analyzed separately.

The analyses will be descriptive. No formal testing of statistical hypotheses is planned in this open-label, single-arm trial.

Descriptive statistics will be performed for continuous variables using the number of available observations, mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarized as the number (percentage) of patients.

Time-to-event variables will be analyzed using the Kaplan-Meier method. Median with log-log confidence intervals (CIs), Q1 (25^{th} percentile) and Q3 (75^{th} percentile) will be presented.

Statistical analyses will be performed using SAS software or other validated statistical software as required. Further details will be provided in the Statistical Analysis Plan.

9.2 Analysis sets

9.2.1 Safety population

All patients exposed to at least one dose of SOT102. All safety analyses will be performed on the safety population.

9.2.2 PK population

All PK-evaluable patients. Evaluation of PK will be performed on the PK population.

9.2.3 DLT-evaluable patients (defined for Part A and Part B only)

The DLT-evaluable patients are defined as in section 4.1.1. This population will be used to assess DLT incidence and to estimate the MTD.

9.2.4 Efficacy population

All patients exposed to at least one dose of SOT102 who had at least one evaluable tumor assessment per RECIST 1.1 after the initiation of SOT102 treatment. This will be the main population for efficacy exploration.

9.3 Statistical analyses

9.3.1 Part A (SOT102 monotherapy, dose escalation) and Part B (SOT102 combination with first-line SoC treatment, dose escalation)

9.3.1.1 Primary endpoint analysis

The incidence of DLTs (in DLT-evaluable patients, see section 4.1.1) by dose level and schedule will be tabulated. The MTD will be determined per Protocol definition. The RP2D will be selected as described in 4.1.1.2. The details will be provided in the DEC Charter.

9.3.1.2 Secondary endpoints analysis

9.3.1.2.1 Safety analyses

9.3.1.2.1.1 Treatment-emergent AEs

AEs will be presented by preferred term (PT) nested within a primary system organ class according to the Medical Dictionary for Regulatory Activities. A TEAE is defined as an AE that:

- emerges at SOT102 treatment start or afterwards, having been absent at the time of pre-treatment (screening), or
- re-emerges at SOT102 treatment start or afterwards, having been present at the time of pre-treatment (screening), or
- worsens in severity at SOT102 treatment start or afterwards relative to the pre-treatment state if the AE is continuous.

Only those AEs that were treatment-emergent will be included in the summary tables. All AEs, treatment-emergent or otherwise, will be presented in the patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and PT. A patient will be counted only once within a system organ class and PT, even if the patient experienced more than one TEAE within a particular system organ class and PT. The number (percentage) of patients with TEAEs will also be summarized by maximum severity (NCI CTCAE grades) and by relationship to SOT102, and, in Part B and Part D, to first-line SoC treatment (Suspected [related] and Not suspected [not related]).

9.3.1.2.1.2 Laboratory values and vital signs

Laboratory results will be summarized using Système International (SI) units as appropriate. Actual value and change from baseline will be explored using descriptive statistics.

9.3.1.2.2 Efficacy analyses

CT or MRI tumor assessments prior to or at the date of initiation of further-line therapy will be used for the evaluation of tumor response. As defined by RECIST 1.1, skin lesions greater than 1 cm may be used for disease evaluation.

All analyses will be descriptive. The evaluation of CLDN18.2 expression status and gastrectomy status (gastric/GEJ adenocarcinoma only) will be taken into account. The change from baseline in overall tumor burden will be described for individual patients. The tumor responses will be tabulated.

9.3.2 Part C (SOT102 monotherapy, cohort expansion)

9.3.2.1 Primary endpoint analysis

9.3.2.1.1.1 Objective response rate

The ORR will be defined as the number of complete responses and partial responses from all evaluable best overall responses (BORs). ORR will be analyzed descriptively by counts and percentages, together with 95% Wald CIs.

The BOR will be evaluated from the first post-baseline tumor assessment until progression or death of patient. Complete and partial response must be confirmed by a subsequent scan, 4 weeks later at the earliest. Stable disease must last at least 6 weeks since the baseline scan; if not, at least one follow-up scan is required to declare stable disease.

9.3.2.2 Secondary endpoints analysis

9.3.2.2.1 Safety analyses

9.3.2.2.1.1 Treatment-emergent AEs

The analysis of TEAEs will follow the definitions of the analyses for this endpoint in Part A and Part B.

9.3.2.2.1.2 Laboratory values and vital signs

Laboratory results will be summarized using SI units as appropriate. Actual value and change from baseline will be explored using descriptive statistics.

9.3.2.2.2 Efficacy analyses

Only CT or MRI tumor assessments prior to or at the date of initiation of further-line therapy will be used for the evaluation of tumor response.

9.3.2.2.2.1 Duration of response

The DoR will be defined as time from the first achieved response (complete or partial, confirmed) until the first date of radiological progression or death.

Patients with missing data will be censored/considered as having an event as specified below:

Situation	**Date of event or censoring**	**Outcome**
No progression, no death. No start of new anticancer therapy.	Date of the last evaluable tumor assessment.	Censored
No progression, no death. Start of new anticancer therapy.	Date of the last tumor assessment with non-progression before the start of new anticancer therapy.	Censored
Progression or death after one missed adequate tumor assessment.	Date of progression or death, whichever is earliest (if both occur).	Event
Progression or death after more than one missed adequate tumor assessments.	Date of the last evaluable tumor assessment.	Censored

The DoR will be summarized using a standard set of summary statistics for time-to-event data.

9.3.2.2.2.2 Progression-free survival

PFS will be defined as the time from trial enrollment until the first date of radiological progression or death.

Patients with missing data will be censored/considered as having an event as specified below:

Situation	**Date of event or censoring**	**Outcome**
Incomplete or no baseline tumor assessment.	Eligibility.	Censored
Start of new anticancer therapy.	Date of the last tumor assessment with non-progression before the start of new anticancer therapy.	Censored
Death before the first disease progression assessment.	Date of death.	Event
Death between adequate tumor assessment visits.	Date of death.	Event
Progression or death after one missed adequate tumor assessment.	Date of progression or death, whichever is earliest (if both occur).	Event
Progression or death after more than one missed adequate tumor assessments.	Date of the last evaluable tumor assessment.	Censored
No progression, no death.	Date of the last evaluable tumor assessment.	Censored

PFS will be summarized using a standard set of summary statistics for time-to-event data.

9.3.2.2.2.3 Overall survival

OS will be defined as the time from eligibility verification until the date of death. Patients who do not die will be censored at the date the patient was last known to be alive.

OS will be summarized using a standard set of summary statistics for time-to-event data.

9.3.2.2.2.4 Clinical benefit rate

Clinical benefit rate will be defined as the number of complete responses, partial responses, and stable diseases from all evaluable BORs.

Clinical benefit rate will be summarized by counts and percentages, along with 95% Wald CIs.

9.3.3 Part D (SOT102 combined with first-line SoC treatment, cohort expansion)

Part D primary and secondary analyses will follow the definitions of Part C analyses.

9.4 Interim analysis

No interim analyses are planned in this trial.

9.5 Sample size determination

9.5.1 Part A (SOT102 monotherapy, dose escalation)

A 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included. Assuming 26 patients have been enrolled prior to this Protocol Amendment and expected enrollment upon trial restart of additional three patients at dose level 2, followed by two dose levels per 6 patients and additional patients for confirmation of the RP2D (acknowledging that at least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion Part C is initiated), the total number of assumed evaluable patients is 47. Assuming 8 patients needed for replacement, the estimated number of patients is 55.

9.5.2 Part B (SOT102 combined with first-line SoC treatment, dose escalation)

A 3+3 design dose escalation will be applied until the MTD is identified. Therefore, 3 to 6 DLT-evaluable patients per dose level will be included. Assuming 5 patients have been enrolled prior to this Protocol Amendment and expected enrollment upon trial restart (only pancreatic cohort) of one dose level per three patients, two dose levels per 6 patients and additional patients for confirmation of the RP2D (acknowledging that at least 6 DLT-evaluable patients will be included to assess the RP2D before the respective expansion parts D is initiated), the total number of assumed patients is 26. Assuming 6 patients needed for replacement, the estimated number of patients per cohort is 32.

9.5.3 Part C (SOT102 monotherapy, cohort expansion) and Part D (SOT102 combination with first-line SoC treatment, cohort expansion)

Part C and Part D are planned to describe the efficacy and safety of SOT102 as monotherapy and in combination with first-line SoC treatment. No statistical testing is planned, only descriptive analyses will be performed. Forty patients in each part and in each indication should provide an adequate number of patients for preliminary efficacy exploration and safety assessment.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and trial oversight considerations

10.1.1 Regulatory and ethical considerations

The Protocol, ICF, and appropriate related documents must be reviewed and approved by an IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted and functioning in accordance with ICH Guideline E6 Good Clinical Practice (GCP)[33] and any local regulations, and by the competent authority (CA). Any Protocol Amendment or revision to the ICF will be resubmitted to the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted and to the CA for review and approval, except for changes involving only logistical or administrative aspects of the trial (e.g., change of CRAs, change of telephone numbers). Documentation of IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted compliance with ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of trial approval from the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted must be sent to the principal investigator or, if regionally required, the head of the medical institution with a copy to the sponsor before trial start and the release of trial interventions to the site by the sponsor or its designee. If the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted decides to suspend or terminate the trial, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of trial suspension or termination by the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted to the sponsor.

Trial progress is to be reported to IRBs/IECs (in the US)/ECs (in the EU)/equivalent committees (outside the US and EU) constituted and to CAs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted, s/he will forward a copy to the sponsor at the time of each periodic report.

The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted (or if regionally required, the investigator and the relevant IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted via the head of the medical institution) and the CA of any reportable AEs per ICH guidelines and local IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted standards of practice. Upon completion of the trial, the investigator or sponsor will provide the IRBs/IECs (in the US)/ECs (in the EU)/equivalent committees (outside the US and EU) constituted and the CAs with a brief report of the outcome of the trial, if required.

At the end of the trial, the sponsor will notify the IRBs/IECs (in the US)/ECs (in the EU)/equivalent committees (outside the US and EU) constituted and CAs as regionally required.

This trial will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to applicable regulatory requirements, and in accordance with the current version of the Declaration of Helsinki and ICH guidelines on GCP.

10.1.2 Financial disclosure

Information on potential financial interests will be provided by all participating investigators. This information will be collected by the sponsor (or a delegated party) before the initiation of the clinical trial, during the course of the clinical trial whenever the financial interests may change, and for a period of one year after the completion of the clinical trial, or termination of a particular individual's participation in this trial.

10.1.3 Informed consent process

Written informed consent will be given by each patient before any procedure of this clinical trial is performed. The process of obtaining the informed consent must comply with applicable ICH GCP E6 guidelines as implemented in EU guidelines and national regulatory requirements.

It is the responsibility of the investigator that patients are clearly and fully informed about the purpose of the clinical trial, its potential risks and benefits, and other critical issues regarding the clinical trial, in which the patient volunteers to participate, before undergoing any clinical trial-specific procedure.

The IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted-approved written ICF, which complies with the above-mentioned regulations, will be provided to each patient. The patient should be given ample time to read and to understand the ICF, and to get the answers to any inquiry related to the clinical trial they may have. The ICF must be signed personally by the patient or their legally acceptable representative, and subsequently by the delegated investigator who obtains the consent. The patient will be provided with a fully signed ICF printout, and with any other written information, before their participation in the clinical trial.

The process of obtaining informed consent must be documented in the patient's source documents.

The sponsor will provide the investigator with a master ICF that complies with ICH GCP guidelines and regulatory requirements and is considered appropriate for this clinical trial. Any changes to this master ICF suggested by the investigator must be agreed to by the sponsor before being submitted to the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted. A copy of the approved version, together with all accompanying approvals, must be provided to the sponsor.

The ICF and any other information provided to patients are subject to changes and revisions whenever important new information relevant to patients' willingness to continue participation in the clinical trial becomes available. Once the IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted approval/favorable opinion on this new information is obtained, the delegated investigator should inform each patient about this newly emerging information as soon as possible. All procedures and regulations to be followed and mentioned above apply also to this scenario, and this process must also be documented in the patient's source documents.

10.1.4 Data protection

In order to ensure that personal information of each patient is kept confidential and protected, names and any other information that allow direct identification of a patient will not be in the eCRFs or included in any records or samples provided to the sponsor or sponsor's authorized representatives; such information will be pseudonymized, i.e., all such information will be replaced by a specific code (patient number) assigned by the sponsor and all patients will be identified in eCRFs or any other records or samples by a patient number only.

The personal information collected for the purposes of this trial will be held by the trial sites, the sponsor and sponsor's authorized representatives, which together are responsible for processing of personal information in accordance with the General Data Protection Regulation (EU) 2016/679 and any corresponding local legislation.

The sponsor and its authorized representatives will analyze and use the personal information they receive for the purposes of this trial only. These include:

- checking patients' suitability to take part in the trial,
- monitoring patients' health during treatment with SOT102 as monotherapy and in combination with first-line SoC treatment,
- comparing and pooling trial results,
- establishing whether SOT102 as monotherapy and in combination with first-line SoC treatment meets the appropriate standards of safety set by the authorities,
- establishing whether SOT102 as monotherapy and in combination with first-line SoC treatment is effective,
- supporting the clinical development of SOT102 as monotherapy and in combination with first-line SoC treatment,
- supporting the licensing application for regulatory approval of SOT102 as monotherapy and in combination with first-line SoC treatment anywhere in the world,
- supporting the marketing, distribution, sale, and use of SOT102 as monotherapy and in combination with first-line SoC treatment anywhere in the world,
- complying with specific regulations governing clinical trials.

Participation of patients in this trial is voluntary and they may withdraw from the trial at any time by informing the investigator. Their participation in the trial will then end and the trial personnel will stop collecting personal information from the patients, but the sponsor will need to retain and use the pseudonymized personal information and associated research results that have already been collected from the patient. The sponsor must do this to comply with its legal and regulatory obligations, to maintain the scientific integrity of the trial, and to complete the marketing authorization process for SOT102 as monotherapy and in combination with first-line SoC treatment. It may be necessary to retain certain aspects of pseudonymized (coded) personal information for at least 25 years following the end of the trial to comply with applicable laws and regulatory requirements and to ensure the scientific integrity of the trial.

If necessary for the trial purposes mentioned above, the sponsor may communicate such pseudonymized personal information to third parties (such as service providers, contractors, and research institutions that support the trial) and regulatory or other governmental agencies that need to check the results of the trial.

These third parties may be located in countries of the European Economic Area (EEA), in the US, and in other countries that are outside of the EEA. Some non-EEA countries may not offer the same level of privacy protection. However, the sponsor will keep personal information it receives as confidential as possible within the limits of the law. The sponsor will implement appropriate contractual measures, including the standard data protection contractual clauses, to ensure that the relevant recipients outside the EEA provide an adequate level of protection to personal information as set out in this form and as required by applicable law.

The sponsor, either alone or together with other researchers, may publish or present the results of the trial; however, personal information will not be disclosed in any publication or presentation.

All persons have certain rights to gain access to and correct any inaccuracies in the personal information held about them. In certain circumstances, they can also request restriction of processing of their personal information, object to certain types of processing of their personal information, request their personal information be erased and have their personal information provided to them or a third party in a digital format. The sponsor shall comply with the above requests to the fullest extent consistent with other legal and regulatory obligations and where required by law.

Personal data cannot be erased, even after patients finish or terminate their participation in the trial, in order to guarantee the validity of the clinical research and to comply with statutory duties and drug authorization requirements.

Representatives from government agencies, the local EC and sponsor or its authorized representatives may also need access to medical records and trial records for the purpose of checking data collected for the trial.

The sponsor shall process all personal information of the patients in the trial in accordance with the General Data Protection Regulation (EU) 2016/679, any applicable local legislation and the internal data protection policies reflecting organizational and technical arrangements to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and personal data processed. The organizational and technical measures introduced by the sponsor in relation to a protection of personal information of the patients involve the above-mentioned pseudonymization of personal information, appropriate controls to restrict its employees access to the personal information, a physical access control to any premises where the personal information is stored, an electronic access and system control logging for any systems containing personal information, data entry and data transfer control, availability control (back-up and recovery concept), network protection including firewalls and penetration testing procedures for regular testing, industry-standard security policies and procedures including assessment and evaluation of processes and regular training procedures. In the event of any security breach, the incident management procedures would be implemented, and the sponsor would notify such breach as applicable.

10.1.5 Organizational structure of the trial

The sponsor of the clinical trial, SOTIO Biotech a.s, may delegate certain tasks to designees, e.g., a contract research organization (CRO) or other third-party vendors. A list of such designated collaborators, including their contact details, will be documented in the investigator's manuals/Investigator Site File.

10.1.6 Dissemination of clinical trial data

By signing the Protocol (INVESTIGATOR'S DECLARATION), every participating investigator agrees to keep all information and results concerning the clinical trial and the investigational product strictly confidential. The confidentiality obligation also applies to all personnel involved at the investigational site.

10.1.7 Risk management and quality assurance

10.1.7.1 Data quality assurance

An eCRF is required and must be completed for each patient by qualified and authorized personnel. All data in the eCRF must reflect the corresponding source document. Any correction to entries made in the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the Protocol for the purposes of the trial should be collected. The investigator must sign the eCRFs.

10.1.8 Trial monitoring, access to source documentation, and data retention

Before trial initiation, at the investigators' meeting or during the Site initiation visit, a representative of the sponsor or a CRO will review the Protocol and eCRFs with the site staff. During the clinical trial, delegated CRA will oversee the progress of the clinical trial and will visit the site regularly to verify the completeness of patient records, reliability and accuracy of entries in eCRFs, the site's adherence to the Protocol and GCP, the progress of enrollment, and that trial interventions are being stored, dispensed, and accounted for according to specifications. The CRA will also verify that the safety and rights of the patients are not compromised. Key clinical trial personnel must be available to assist the CRA during these visits.

For each patient recruited into the clinical trial, the investigator must maintain source documents, which should consist of case and visit notes (hospital or outpatient clinic medical records) containing demographic and medical information, laboratory data, and results of any other tests or assessments. All information in eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original of the ICF signed by the patient or their legally acceptable representative (the second signed original must be given to the patient).

The investigator must allow the CRAs or other delegated representatives to visit all site locations, and to allow direct access to all clinical trial-related documentation and data, as well as to the patient's source documents and other charts and records.

Monitoring standards of the sponsor require full verification for the presence of a fully signed and dated ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of data that will be used for all primary and safety variables. Additional verification of the consistency of the source data with the eCRFs will be performed according to a clinical trial-specific Monitoring Plan.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

The trial may also be evaluated by any other designee delegated by the sponsor, IRB/IEC (in the US)/EC (in the EU)/equivalent committees (outside the US and EU) constituted representatives, or by any independent institutional or government inspectors, who must be given direct access to the same as mentioned above. Such a possibility must also be clearly mentioned in the patient's ICF.

The investigator must promptly notify the sponsor or its delegated representatives any time the request for inspection is raised by any regulatory agency, and provide copies of all documentation received from such an agency.

The investigator or institution must retain all trial-related records, materials provided by the sponsor or its delegated collaborators, copies of eCRFs, and source documents of patients for a specified period of time. This period of time is derived from the locally applicable regulation guidelines or requirements, institution procedures, or requirements stipulated by the sponsor or its representatives, whichever is longer.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator must contact the sponsor, allowing the sponsor the option of permanently retaining the trial records.

10.1.9 Publication policy

The results of this clinical trial will be published and/or presented at scientific meetings in their totality in a timely manner. No single institution presentation/publication of data is foreseen if not agreed by the sponsor and all relevant investigators of the trial. Any formal publication of clinical trial results will be a collaborative effort between the sponsor and the investigator(s). All manuscripts or abstracts will be reviewed and approved in written by the sponsor before submission. The sponsor may request a delay in publication if there are important intellectual property concerns but does not have the right to suppress the publication of the clinical trial results indefinitely.

Authorship will be determined by mutual agreement, with the coordinating investigator of this clinical trial being given priority for first authorship. Publications will include all clinical trial investigators in the order of their relative patient contribution, taking into account also contributions during Protocol development and data analyses.

10.1.10 Committees

10.1.10.1 Independent committees

10.1.10.1.1 Data monitoring committee

An IDMC will be established for trial Part C and Part D to safeguard the interest and safety of the patients participating in the trial. The IDMC will provide independent review and assessment of the interim efficacy and safety results on a regular basis in a systematic manner. The efficacy data will include descriptive analysis as described in the IDMC Charter.

The membership, key responsibilities of the IDMC, and corresponding procedures will be defined in the IDMC Charter.

10.1.11 Future research

Biological samples collected during this trial may be stored for future research by the sponsor. Storage conditions will be in compliance with the standards for repositories of biological samples, according to the "Recommendation CM/Rec (2016)6 of the Committee of Ministers to member States on research on biological materials of human origin".[34]

The repository will have independent monitoring that will guarantee protection of the data and the patients' interests (also see section 10.1.4). Except for contractors of the sponsor, the samples will not be transferred to third parties, and they will not be sold to third parties. The exploratory studies that will be conducted with the samples will undergo a rigorous independent review evaluating both ethical and scientific aspects.

10.2 Appendix 2: Hy's law

Drugs are likely to cause a high rate (10-50%) of fatal liver injury or need for transplant in patients with acute hepatocellular injury sufficient to cause jaundice. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury (not cholestatic injury) with jaundice.

Hy's law cases have three components:

- The drug causes hepatocellular injury, generally defined as an elevated ALT or AST by 3-fold or greater above the ULN. Often with aminotransferases much greater (5-10×ULN).
- Among patients showing such aminotransferase elevations, they also have elevation of their serum total bilirubin of greater than 2×ULN, without findings of cholestasis (defined as serum alkaline phosphatase (ALP) activity less than 2×ULN).

No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.

10.3 Appendix 3: Cockcroft-Gault formula

For males, creatinine clearance is estimated using the Cockcroft-Gault formula as follows:

Creatinine clearance = [(140 − age) × weight]/(72 × serum creatinine)

Where age is in years, weight is in kilograms, and serum creatinine is in mg/dL. Actual, not ideal weight is to be used.

For females, creatinine clearance is estimated by multiplying the result of the above formula by 0.85.

10.4 Appendix 4: Laboratory parameters to be assessed

10.4.1 Coagulation

Coagulation tests will include prothrombin time and INR.

10.4.2 Hematology

- Leukocytes
- Erythrocytes
- Hemoglobin

- Hematocrit
- Platelets
- Differential:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils

Treatment decisions will be based on local laboratory results.

10.4.3 Clinical chemistry

- ALT
- Albumin, serum albumin*
- ALP
- Amylase
- AST
- Bilirubin
- Blood urea nitrogen or blood urea
- Calcium
- Creatinine
- Glucose (fasting)
- Lactate dehydrogenase
- Lipase
- Magnesium
- Potassium
- Serology (HIV, HBV-positive patients only)
- Sodium
- TSH (for Part B gastric only)
- Urea*

* Parameters to be measured on D8 of each cycle

Note: For country-specific requirements, see section 10.8.

10.4.4 Urinalysis

- Leukocytes
- Blood
- Glucose
- Ketones
- pH
- Protein

- Specific gravity
- Urine leukocyte esterase

Urine analysis must be performed in a laboratory. Urine dipstick test alone is not allowed. Entry limit at screening is grade 1 proteinuria (<1 g/24 hours; see section 5.1.1). Urinalysis will be performed prior to each day 1 of each cycle and in case of detection of ≥100 mg/dL proteinuria, a 24-hour urine analysis will have to be performed (prior to the start of SOT102 treatment) to document 24-hour proteinuria levels.

10.5 Appendix 5: List of medications requiring special caution

Medications that may prolong the QT interval are:[35]

Known risk	Conditional risk	Possible risk
Amiodarone	Amantadine	Alfuzosin
Azithromycin	Amisulpride	Aripiprazole
Chlorpromazine	Amitriptyline	Asenapine
Ciprofloxacin	Fluoxetine	Atazanavir
Citalopram	Furosemide	Clomipramine
Domperidone	Hydrochlorothiazide	Clozapine
Donepezil	Hydroxychloroquine	Imipramine
Escitalopram	Indapamide	Lithium
Fluconazole	Ivabradine	Mirtazapine
Haloperidol	Metoclopramide	Nortriptyline
Levofloxacin	Pantoprazole	Olanzapine
Levomepromazine	Paroxetine	Paliperidone
Methadone	Quetiapine	Rilpivirine
Ondansetron	Ritonavir	Risperidone
Sulpiride	Sertraline	Saquinavir
	Trazodone	Tamoxifen
	Ziprasidone	Tetrabenazine
		Trimipramine
		Venlafaxine

Medications that may induce CYP2C8, CYP2C9, and/or CYP3A4/CYP3A are:[36]

Cytochrome	Strong induction	Moderate induction	Weak induction
CYP2C8		Rifampin	
CYP2C9		Enzalutamide Rifampin	Apalutamide Aprepitant Carbamazepine Ritonavir
CYP3A	Apalutamide Carbamazepine Enzalutamide Mitotane	Bosentan Efavirenz Etravirine Phenobarbital	Armodafinil Modafinil Rufinamide

Cytochrome	Strong induction	Moderate induction	Weak induction
	Nevirapine Rifampin St. John's wort	Primidone	

Medications that may inhibit CYP2C8, CYP2C9, CYP2D6, and/or CYP3A4/CYP3A are:[36]

Cytochrome	Strong inhibition	Moderate inhibition	Weak inhibition
CYP2C8	Gemfibrozil	Clopidogrel Deferasirox Teriflunomide	Trimethoprim
CYP2C9		Amiodarone Fluconazole Miconazole Piperine	Diosmin Disulfiram Fluvastatin Fluvoxamine Voriconazole
CYP2D6	Bupropion Fluoxetine Paroxetine Quinidine Terbinafine	Abiraterone Cinacalcet Duloxetine Lorcaserin Mirabegron	Amiodarone Celecoxib Cimetidine Clobazam Cobicistat Escitalopram Fluvoxamine Labetalol Ritonavir Sertraline Vemurafenib
CYP3A4	Boceprevir Clarithromycin Cobicistat Danoprevir and ritonavir Elvitegravir and ritonavir Grapefruit juice	Aprepitant Ciprofloxacin Conivaptan Crizotinib Cyclosporine Diltiazem	Chlorzoxazone Cilostazol Cimetidine Clotrimazole Fosaprepitant Istradefylline

Cytochrome	Strong inhibition	Moderate inhibition	Weak inhibition
	Idelalisib	Dronedarone	Ivacaftor
	Indinavir and ritonavir	Erythromycin	Lomitapide
	Itraconazole	Fluconazole	Ranitidine
	Ketoconazole	Fluvoxamine	Ranolazine
	Lopinavir and ritonavir	Imatinib	Ticagrelor
	Nefazodone	Tofisopam	
	Nelfinavir	Verapamil	
	Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)		
	Posaconazole		
	Ritonavir		
	Saquinavir and ritonavir		
	Telaprevir		
	Telithromycin		
	Tipranavir and ritonavir		
	Troleandomycin		
	Voriconazole		

Medications that are substrates of CYP2D6, and/or CYP3A are:[36]

Cytochrome	Sensitive substrates	Moderate sensitive substrates
CYP2D6	Atomoxetine	Encainide
	Desipramine	Imipramine
	Dextromethorphan	Metoprolol
	Eliglustat	Propafenone
	Nebivolol	Propranolol
	Nortriptyline	Tramadol
	Perphenazine	Trimipramine
	Tolterodine	S-venlafaxine
	R-venlafaxine	
CYP3A	Alfentanil	Alprazolam
	Avanafil	Aprepitant

Cytochrome	Sensitive substrates	Moderate sensitive substrates
	Budesonide	Atorvastatin
	Buspirone	Colchicine
	Conivaptan	Eliglustat
	Darifenacin	Pimozide
	Darunavir	Rilpivirine
	Dasatinib	Rivaroxaban
	Dronedarone	Tadalafil
	Ebastine	
	Eletriptan	
	Eplerenone	
	Everolimus	
	Felodipine	
	Ibrutinib	
	Indinavir	
	Lomitapide	
	Lovastatin	
	Lurasidone	
	Maraviroc	
	Midazolam	
	Naloxegol	
	Nisoldipine	
	Quetiapine	
	Saquinavir	
	Sildenafil	
	Simvastatin	
	Sirolimus	
	Tacrolimus	
	Ticagrelor	
	Tipranavir	
	Tolvaptan	
	Triazolam	
	Vardenafil	

10.6 Appendix 6: Abbreviations

Abbreviation	Term
5-FU	Fluorouracil
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AST	Aspartate transaminase
AxMP	Auxiliary medicinal product
BOR	Best overall response
BRCA	Breast cancer gene
CA	Competent authority
CD	Cluster of differentiation
CI	Confidence interval
CLDN18.2	Claudin 18 splice variant 2
CRA	Clinical research associate
CRO	Contract research organization
CT	Computed tomography
CYP2C8	Cytochrome P2C8
CYP2C9	Cytochrome P2C9
CYP2D6	Cytochrome P2D6
CYP3A(4)	Cytochrome P3A(4)
CYP450	Cytochrome P450
DEC	Dose Escalation Committee
DEM	Dose Escalation Meeting
DLn	Dose level number
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DPD	Dihydropyrimidine dehydrogenase
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDA	Ethylene diamine
EEA	European Economic Area
EU	European Union
FFPE	Formalin-fixed paraffin-embedded

Abbreviation	Term
FOLFIRINOX	Leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
HBV	Hepatitis B
HCV	Hepatitis C
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IB	Investigator's Brochure
ICF	Informed Consent Form
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
LVEF	Left ventricular ejection fraction
mFOLFOX6	Modified oxaliplatin + leucovorin + 5-fluorouracil-containing chemotherapy regimen
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scanning
Nab-paclitaxel	Paclitaxel protein-bound
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PT	Preferred term
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SaO_2	Arterial oxygen saturation
SI	Système International
SmPC	Summary of Product Characteristics

Abbreviation	Term
SoC	Standard of care
SOT102	CLDN18.2-specific monoclonal antibody SOT102.1 conjugated to [redacted]
STD_{10}	Severely toxic dose in 10% of the animals
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limits of normal
US	United States of America
WOCBP	Woman of childbearing potential

**Abbreviations of commonly used weight, height, and volume measures are not listed above.*

10.7 Appendix 7: Protocol Amendment history

The PROTOCOL AMENDMENT SUMMARY OF CHANGES for the current amendment is located directly before the TABLE OF CONTENTS.

10.7.1 Amendment 4 (08Mar2024): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment 4
1	The population of the trial was changed to include only patients with pancreatic cancer in the future. Gastric/GEJ cohorts were removed from parts C and D. Relevant information was modified throughout the document. Sample size was updated accordingly. For patients ongoing in gastric cohort, notes specifying time windows for some assessments have been updated to reflect that no SOT102 will be administered.	Enrollment of patients with gastric/GEJ cancer was stopped by the decision of the sponsor. Due to gastric/GEJ patients being enrolled and continuing in Part B at the time of the Protocol update, relevant information has been kept in the Protocol. SOT102 will not be administered to patients anymore, some assessments do not need to be made or do not need to be made within a related time window.	Throughout the document; 1.3.2 Schedule of activities Part B gastric;
2	Introduction of premedication with corticosteroids a day before, on the day of (at least 1 hour prior), and the day after SOT102 administration	To reflect renal toxicity safety signals, and to prevent and/or ameliorate any inflammatory stimulation of podocytes	1.1 Synopsis; 1.3.1, Schedule of activities Part A; 1.3.3 Schedule of activities Part B pancreatic; 1.3.4 Schedule of activities Part C;1.3.5 Schedule of activities Part D pancreatic; 6.1.1 SOT102 (all trial parts);
3	Assessment of clinical chemistry with focus on renal function, urinalysis and creatinine clearance added on day 8 of each cycle in parts A and B. Urine spot analysis added before SOT102 administration and every day 8 of each cycle in parts A and B. Assessment of clinical chemistry, urinalysis, and creatinine clearance added on day 21 in Part B.	To monitor renal function of patients more closely	1.3.1, Schedule of activities Part A; 1.3.3 Schedule of activities Part B pancreatic; 10.4.3 Clinical chemistry; 10.4.4 Urinalysis
4	For LVEF and tumor assessments: assessments obtained prior the ICF signature as a part or standard of care/routine practice may be used for screening and trial purposes	To allow use of earlier assessments for the purpose of the trial	1.3.1, Schedule of activities Part A; 1.3.2 Schedule of activities Part B gastric; 1.3.3 Schedule of activities Part B pancreatic; 1.3.4 Schedule of activities Part C; 1.3.5 Schedule of activities Part D

Change number	Description of change	Rationale for change	Section in Amendment 4
			gastric; 1.3.6 Schedule of activities Part D pancreatic
5	Clarification added that urine dipstick cannot be used for assessment of urinalysis	To inform investigators not to use qualitative assessments of urinalysis.	1.3.1, Schedule of activities Part A; 1.3.2 Schedule of activities Part B gastric; 1.3.3 Schedule of activities Part B pancreatic; 1.3.4 Schedule of activities Part C; 1.3.5 Schedule of activities Part D gastric; 1.3.6 Schedule of activities Part D pancreatic; 10.4.4 Urinalysis
6	Addition of a 2-hour window for ECG at 24 hours after the end of SOT102 infusion in cycles 1 and 3	To add time allowance for measurement of ECG after drug administration	1.3.1, Schedule of activities Part A; 1.3.2 Schedule of activities Part B gastric; 1.3.3 Schedule of activities Part B pancreatic; 8.2.4 Electrocardiography
7	Esophagogastroduodenoscopy at screening is to be done up to 6 months before cycle 1 day 1 in parts C and D	To clarify screening/eligibility conditions	1.3.4 Schedule of activities Part C; 1.3.5 Schedule of activities Part D gastric; 1.3.6 Schedule of activities Part D pancreatic
8	Addition of PK samples to be collected at occurrence of grade ≥3 AE and at the time SOT102 treatment resumes and at occurrence of grade 4 AE Addition of PK sample to be collected at time of disease progression Addition of dense PK sampling to cycle 5 of SOT102 therapy	To collect PK data at the time of occurrence of toxicity and at the time the treatment is resumed To allow more precise assessment of presence and role of ADA To obtain more precise PK data at a later time of SOT102 exposure	1.3.6 PK and ADA sampling (SOT102), Part A and Part B; 1.3.7 PK and ADA sampling (SOT102), Part C and Part D
9	Addition of ADA sample collection at the time of disease progression in parts A and B	To explore the dynamics of ADA at the time of disease progression and also to investigate if those ADAs are potentially neutralizing at that time	1.3.6 PK and ADA sampling (SOT102), Part A and Part B
10	Definition of DLT-evaluable patient in Part B extended with information on SoC	To include patients who also receive corresponding SoC treatment	4.1.1 Dose escalation plan (Part A and Part B)
11	Grade ≥2 serum creatinine elevation and grade ≥2 proteinuria added to the list of AEs considered DLTs	To reflect renal toxicity safety signals and ensure safety of patients	4.1.1.1 Dose-limiting toxicities definitions

Change number	Description of change	Rationale for change	Section in Amendment 4
12	End of trial definition updated to include information on trial start. Section 10.1.8 Trial start and closure removed.	To better define trial start	4.4 Trial and site start and closure
13	Inclusion criteria on availability of tumor biopsy samples in sections with trial parts specifics were merged into criterion no. 13	To clarify screening/eligibility conditions	5.1.1 Inclusion criteria applicable to all trial parts; 5.1.2 Inclusion criteria specific to Part A; 5.1.3 Inclusion criteria specific to Part B; 5.1.4 Inclusion criteria specific to Part C; 5.1.5 Inclusion criteria specific to Part D
14	Exclusion criterion no. 1 on prior therapy with CLDN18.2-directed agents removed	To clarify screening/eligibility conditions	5.2.1 Exclusion criteria applicable to all trial parts
15	Exclusion criterion no. 19 updated to include information on completion of full vaccination series if feasible	To provide more clarity to investigators	5.2.1 Exclusion criteria applicable to all trial parts
16	Exclusion criterion on time since last transfusion before cycle 1 day 1 added to all trial parts (no. 17) and related restriction removed from inclusion criterion no. 3.1	To clarify screening/eligibility conditions	5.1.1 Inclusion criteria applicable to all trial parts; 5.2.1 Exclusion criteria applicable to all trial parts
17	Clarification added to definition of screen failures that these are patients who fail to meet the eligibility criteria	To provide better guidance to investigators	5.4 Screen failures
18	Addition of reporting of medication errors, including abuse, misuse and/or over/underdose	To comply with regulatory guidance	6.4 Trial intervention compliance
19	Rules for dose modification in case of a grade ≥3 AE clarified	To provide better guidance to investigators	6.5.1 Dose modification and toxicity management of SOT102
20	Clarification on auxiliary medicinal products added	To provide better guidance to investigators and to comply with regulatory guidance	6.8.1 Rescue medication and supportive care
21	NSAIDs and other potentially nephrotoxic medications should be used with caution when administered with SOT102	To provide more safety for patients	6.8.3 Medications requiring caution
22	DLT conditions added to causes for discontinuation of trial intervention	To provide better guidance for investigators	7.1 Discontinuation of trial intervention
23	All safety assessments should be carried out according to standard local institutional practice unless otherwise stated in the Protocol	To provide more clarity to investigators	8.2 Safety assessments
24	Specific timelines for reporting SUSARs replaced with information on the need to follow national safety reporting requirements for reporting	To provide more clarity to investigators	8.3.5 Regulatory reporting requirements for SAEs

Change number	Description of change	Rationale for change	Section in Amendment 4
25	Restrictions for egg and sperm donations after SOT102 treatment added	To provide more safety for patients	8.3.6 Pregnancy
26	Addition of clarification on AE causality assessment	To provide better guidance for investigators	8.3.7.1 Causality
27	Section on tumor biopsy added	To provide more clarity to investigators	8.6 Tumor biopsy
28	Clarification added that skin lesions may be used for disease evaluation as defined by RECIST 1.1	To provide better guidance for investigators	9.3.1.2.2 Efficacy analyses
29	Reporting of neutrophils by automated differential instruments and the final count including segmented and band forms removed	To provide more clarity to investigators	10.4.2 Hematology
30	EudraCT number updated to EUCT number, NCT number added	To update regulatory identifiers	Title page; 1.1 Synopsis
31	Change of sponsor address	Administrative change	Title page
32	Overview of Objectives and Endpoints was converted to a table	For better clarity	3 Objectives and Endpoints
33	Update of contact information or reporting of SAEs/pregnancies. Removal of fax/telephone number for reporting SAEs/pregnancies.	Administrative change	8.3.8.3 Immediately reportable events
34	Minor wording and punctuation corrections	To align Protocol with new regulatory guidance and to improve clarity and readability	Throughout the document

10.7.2 Amendment 3 (27Apr2023): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment 3
1	Trial Protocol synopsis adjusted to follow the CTR recommended order of information	To align format of synopsis with global recommendations (no content change, only updated order of information and addition of Ethical considerations)	1.1 Synopsis
2	A correction was made to the Schedule of activities for Part D pancreatic – body weight is to be collected on D15, not D21	To correct an error	1.3.6 Schedule of activities, Part D pancreatic

Change number	Description of change	Rationale for change	Section in Amendment 3
3	Inclusion criterion no. 12 harmonized between global Amendment 2 (01Sep2022) and local amendment FR-3 (01Sep2022)	To include French local specificity requested by ANSM into one consolidated Protocol	5.1.1 Inclusion criteria applicable to all trial parts; 10.8 Appendix 8: Country-specific requirements/differences
4	Information on country-specific set of laboratory tests to be made was added	To include French local specificity requested by ANSM into one consolidated Protocol	10.4.3 Clinical chemistry; 10.8 Appendix 8: Country-specific requirements/differences
5	Adding the possibility of having the trial assessed by committee equivalent to IRB/IEC/EC (outside the US and EU)	To allow the trial to be conducted outside of US/EU	Throughout the document
6	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document

10.7.3 Amendment FR-3 (01Sep2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment FR-3
1	Objectives and endpoints were updated to include additional analytes in PK analyses	To better characterize the PK of the trial drug	1.1 Synopsis ; 3.1.1 – 3.1.4 Objectives (Part A, Part B, Part C, Part D) ; 3.2.1 – 3.2.4 Endpoints (Part A, Part B, Part C, Part D)
2	A note was modified in Schedule of activities for all parts to day 1 to allow a window of ±1 day starting from cycle 6 (note 14 for Part A and Part B) or cycle 2 (note 15 for Part C and Part D) for dosing of SOT102 and/or first-line SoC treatment; a window of 1 day early was added for the collection of safety laboratory samples starting from cycle 2 for all trial parts (note 16 for Part A and Part B, note 18 for Part C and Part D)	To provide more operational flexibility to trial sites	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D); 6.5.1 Dose modification and toxicity management for SOT102; 6.5.2 Dose modification and toxicity management for first-line SoC treatment; 8.2.5 Clinical safety laboratory assessments
3	Schedule of collection of immunogenicity sampling was clarified for all trial parts	Revised for better clarity	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D)
4	Time period and frequency for collecting AEs/TEAEs was clarified	Revised for better clarity	4.1.1.4.1 Part A; 4.1.1.4.2 Part B; 8.3.2 Time period and frequency for collecting AE, SAE, and other

Change number	Description of change	Rationale for change	Section in Amendment FR-3
			reportable safety event information; 9.3.1.2.1.1 Treatment-emergent AEs
5	Schedule of pregnancy testing during the trial was clarified in Part B pancreatic and Part D pancreatic	Revised according to the AFMPS's request/ recommendation (06Apr2022)	1.3.3 Schedule of activities (Part B pancreatic), 1.3.6 Schedule of activities (Part D pancreatic)
6	Schedule of physical exams, vital signs, biochemistry, urinalysis, creatinine clearance, and ECG determinations was clarified in Part B pancreatic and Part D pancreatic; body weight measurement added to day 15	Revised according to the AFMPS's request/ recommendation (06Apr2022)	1.3.3 Schedule of activities (Part B pancreatic), 1.3.6 Schedule of activities (Part D pancreatic)
7	Schedule of QoL assessments was clarified	Revised for better clarity	1.3.4 – 1.3.6 Schedule of activities (Part C, Part C gastric, Part D pancreatic; 8.1.2 Quality of life assessments (only in Part C and Part D)
8	In schedules of activities for Part A and Part B urine was added to PK sampling. In PK sampling schedule correction was made to specify that for urine, only concentrations will be measured. Urine PK sample collection timing was clarified, a note was added that urine PK sample collection schedule will be specified in the Laboratory Manual.	Revised for better clarity	1.3.1 – 1.3.3 Schedule of activities (Part A, Part B); 1.3.7 PK and ADA sampling (SOT102), Part A and Part B
9	Discontinuation from therapy mandated for patients who develop toxicities qualified as DLTs unless they demonstrate a clear clinical benefit	Revised according to the AFMPS's request/ recommendation (06Apr2022)	4.1.1.1 Dose-limiting toxicities definitions
10	Inclusion criterion 7 was modified to recommend sperm preservation for males	Revised according to the AFMPS's request/recommendation (06Apr2022)	5.1.1 Inclusion criteria applicable to all trial parts
11	Addition of exclusion criterion no. 19 for all trial parts to exclude patients treated with a live or live-attenuated vaccine 30 days before treatment administration; information about not allowing vaccination with live or live-attenuated vaccines	Revised according to the SUKL's recommendation (SUKL RFI 11Feb2022)	5.2.1 Exclusion criteria applicable to all trial parts; 6.8.3 Medications requiring special caution

Change number	Description of change	Rationale for change	Section in Amendment FR-3
	during the trial and within 90 days after the last dose of SOT102 and/or SoC added		
12	Information was added that caution should be exercised when administering trial medication with medications known as substrates of CYP2D6 and CYP3A, when administering trial medication or nab-paclitaxel with QT/QTc interval-prolonging medications; recommendation against use of CYP2C8 and CYP3A4 inducers added for EU in cohorts including nab-paclitaxel	Revised according to the ANSM's request/ recommendation (28Mar2022), AFMPS's request/recommendation (11May2022), and AFMPS's request/ recommendation (06Apr2022)	6.8.3 Medications requiring special caution; 6.8.3.2 Nab-paclitaxel
13	Clarification was added of the timing of radiology assessments throughout the study	Revised for better clarity	8.1.1 Radiologic evaluation of disease
14	ECOG collection moved from section on efficacy measures (8.1.2) to section on safety (8.2.1)	Revised for better clarity	8.2.1 Physical examinations, body height, weight, and surface area, ECOG performance status
15	Information on what needs to be documented in eCRF on AE page specified (Other suspected cause and Other action taken are not to be recorded)	Revised for better clarity	8.3.8.2 Documenting in eCRFs
16	Clarification on sponsor's contractors being excluded from third parties added	Revised for better clarity	10.1.12 Future research
17	List of CYP2D6 and/or CYP3A substrates included in list of medications requiring special caution	Revised according to the AFMPS's request/ recommendation (06Apr2022)	10.5 Appendix 5: List of medications requiring special caution
18	Change of Statistician	Change of personnel	SIGNATURES/PROTOCOL APPROVAL AND RELEASE SOTIO
19	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document

10.7.4 Amendment 2 (01Sep2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment 2
1	Objectives and endpoints were updated to include additional analytes in PK analyses	To better characterize the PK of the trial drug	1.1 Synopsis; 3.1.1 – 3.1.4 Objectives (Part A, Part B, Part C, Part D); 3.2.1 – 3.2.4 Endpoints (Part A, Part B, Part C, Part D)
2	A note was added to the trial design schema to clarify the patient population in Part B and Part D of the trial. In addition, exclusion criterion 20 for Part B and Part D was updated to clarify the same	Revised according to the ANSM's request/ recommendation (28Mar2022)	1.2 Schema; 5.2.3 Exclusion criteria specific to Part B; 5.2.5 Exclusion criteria specific to Part D
3	A note was modified in Schedule of activities for all parts to day 1 to allow a window of ±1 day starting from cycle 6 (note 14 for Part A and Part B) or cycle 2 (note 15 for Part C and Part D) for dosing of SOT102 and/or first-line SoC treatment; a window of 1 day early was added for the collection of safety laboratory samples starting from cycle 2 for all trial parts (note 16 for Part A and Part B, note 18 for Part C and Part D)	To provide more operational flexibility to trial sites	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D); 6.5.1 Dose modification and toxicity management for SOT102; 6.5.2 Dose modification and toxicity management for first-line SoC treatment; 8.2.5 Clinical safety laboratory assessments
4	Monitoring of SaO_2 was added to the assessments to be performed in the trial for all trial parts and all cohorts	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D)
5	Schedule of collection of immunogenicity sampling was clarified for all trial parts	Revised for better clarity	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D)
6	Monitoring of HIV and HBV for HIV and/or HBV-positive patients was added to the assessments to be performed in the trial for all trial parts and all cohorts	Revised according to the ANSM's request/ recommendation (28Mar2022)	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D); 10.4.3 Clinical chemistry
7	Monitoring of AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment and monitoring of concomitant medication was added to the follow-up until disease progression or start of new anticancer therapy in Part A and Part B and the timelines were clarified	Revised according to the ANSM's request/ recommendation (28Mar2022)	1.3.1 – 1.3.3 Schedule of activities (Part A, Part B); 4.1.1.4.1 Part A; 4.1.1.4.2 Part B; 4.1.2.4 Follow-up period (Part A); 4.1.3.4 Follow-up period (Part B); 8.3.2 Time period and frequency for collecting AE, SAE, and other reportable safety event information; 9.3.1.2.1.1 Treatment-emergent AEs
8	Monitoring of LVEF schedule for Part B was aligned with that of Part A; monitoring of LVEF was added to the assessments to be performed at 30 (±5) days after the last	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	1.3.2 – 1.3.6 Schedule of activities (Part B, Part C, Part D)

Change number	Description of change	Rationale for change	Section in Amendment 2
	dose of SOT102 for trial Part B, Part C, and Part D, all cohorts		
9	Schedule of pregnancy testing during the trial was clarified in Part B pancreatic and Part D pancreatic	Revised according to the AFMPS's request/ recommendation (06Apr2022)	1.3.3 Schedule of activities (Part B pancreatic); 1.3.6 Schedule of activities (Part D pancreatic)
10	Schedule of physical exams, vital signs, biochemistry, urinalysis, creatinine clearance, and ECG determinations was clarified in Part B pancreatic and Part D pancreatic; body weight measurement added to day 15	Revised according to the AFMPS's request/ recommendation (06Apr2022) and for better clarity	1.3.3 Schedule of activities (Part B pancreatic); 1.3.6 Schedule of activities (Part D pancreatic)
11	Schedule of QoL assessments was clarified	Revised for better clarity	1.3.4 – 1.3.6 Schedule of activities (Part C, Part C gastric, Part D pancreatic; 8.1.2 Quality of life assessments (only in Part C and Part D)
12	In schedules of activities for Part A and Part B urine was added to PK sampling. In PK sampling schedule correction was made to specify that for urine, only concentrations will be measured. Urine PK sample collection timing was clarified, a note was added that urine PK sample collection schedule will be specified in the Laboratory Manual.	Revised for better clarity	1.3.1 – 1.3.3 Schedule of activities (Part A, Part B); 1.3.7 PK and ADA sampling (SOT102), Part A and Part B
13	ECG measurement schedule was clarified in footnotes 5 and 10 of the schedules of activities for Part A and Part B	Revised according to the ANSM's request/ recommendation (17Jun2022)	1.3.1 – 1.3.3 Schedule of activities (Part A, Part B)
14	Number of patients to be treated at the RP2D before opening expansion cohorts was clarified	Revised according to the ANSM's request/ recommendation (28Mar2022)	4.1.1 Dose escalation plan (Part A and Part B); 4.1.1.2 Maximum tolerated dose and selection of the recommended phase 2 dose; 9.5.1 Part A (SOT102 monotherapy, dose escalation); 9.5.2 Part B (SOT102 combined with first-line SoC treatment, dose escalation)
15	The list of exceptions from DLTs in Protocol section 4.1.1.1 was modified to include grade 3 or higher amylase or lipase not associated with symptoms or clinical manifestations, or radiological evidence of pancreatitis	Revised according to the ANSM's request/ recommendation (17Jun2022)	4.1.1.1 Dose-limiting toxicities definitions

Change number	Description of change	Rationale for change	Section in Amendment 2
16	Discontinuation from therapy mandated for patients who develop toxicities qualified as DLTs unless they demonstrate a clear clinical benefit	Revised according to the AFMPS's request/ recommendation (06Apr2022)	4.1.1.1 Dose-limiting toxicities definitions
17	Communication plan between the sponsor, the investigators, and the subjects in the event of emerging safety issues was updated	Revised according to the ANSM's request/ recommendation (28Mar2022)	4.1.1.6 Communication plan
18	Stopping rules were moved from section 4.1.1.7 to section 5.5 and were updated to include all trial parts and all cohorts. Section 4.1.1.7 was removed.	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's recommendation (11 May 2022)	5.5 Criteria for temporarily delaying enrollment/administration of trial intervention
19	Inclusion criterion 3.7 on serum concentrations of potassium, magnesium, and calcium within normal range was added	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	5.1.1 Inclusion criteria applicable to all trial parts
20	Inclusion criterion 6.2 was modified to specify that a highly effective contraceptive method must be used during the treatment period and for at least 9 months after the last dose of SOT102 or first-line SoC treatment (whichever occurs later).	Revised according to the ANSM's request/ recommendation (28Mar2022)	5.1.1 Inclusion criteria applicable to all trial parts
21	Inclusion criterion 7 was modified to specify that a highly effective contraceptive method must be used by WOCBP partners of male participants and also to recommend sperm preservation for males	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	5.1.1 Inclusion criteria applicable to all trial parts
22	Inclusion criterion 13 for Part A and Part C was moved to the section of criteria applicable to all trial parts (now criterion 12) and the wording was updated to specify that it refers to treatment for locally advanced gastric/pancreatic cancer	Revised for better clarity	5.1.1 Inclusion criteria applicable to all trial parts
23	Exclusion criteria applicable to all trial parts was modified to exclude patient previously treated with anthracyclines at the maximum cumulative dose (exclusion criterion 3)	Revised according to the ANSM's request/ recommendation (17Jun2022)	5.2.1 Exclusion criteria applicable to all trial parts
24	Exclusion criterion 7 was updated to specify that an active infection must be clinically controlled before patient's inclusion in the trial	Revised according to the ANSM's request/ recommendation (28Mar2022)	5.2.1 Exclusion criteria applicable to all trial parts

Change number	Description of change	Rationale for change	Section in Amendment 2
25	Exclusion criterion 11 was updated to specify that patients with NYHA ≥2 heart failure must be excluded from the trial	Revised according to the ANSM's request/ recommendation (28Mar2022)	5.2.1 Exclusion criteria applicable to all trial parts
26	Exclusion criterion 14 was added to exclude patients with bradycardia from the trial	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	5.2.1 Exclusion criteria applicable to all trial parts
27	Exclusion criterion 15 was added to exclude patients with family history of sudden cardiac death before age 50 from the trial	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	5.2.1 Exclusion criteria applicable to all trial parts
28	Addition of exclusion criterion no. 19 for all trial parts to exclude patients treated with a live or live-attenuated vaccine 30 days before treatment administration; information about not allowing vaccination with live or live-attenuated vaccines during the trial and within 90 days after the last dose of SOT102 and/or SoC added	Revised according to the SUKL's recommendation (SUKL RFI 11Feb2022)	5.2.1 Exclusion criteria applicable to all trial parts; 6.8.3 Medications requiring special caution
29	Exclusion criterion 22 was added for Part B and Part D to exclude patients with clinically active inflammatory bowel disease from the trial	Revised according to the ANSM's request/ recommendation (28Mar2022)	5.2.3 Exclusion criteria specific to Part B; 5.2.5 Exclusion criteria specific to Part D
30	Exclusion criterion 25 was added for Part B and Part D gastric cohorts to exclude use of medications known to prolong QT/QTc interval during the trial	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	5.2.3 Exclusion criteria specific to Part B (gastric); 5.2.5 Exclusion criteria specific to Part D (gastric)
31	Exclusion criterion 23 was added for Part B and Part D so as not to authorize the inclusion of patients with pancreatic adenocarcinoma eligible for FOLFIRINOX	Revised according to the ANSM's request/ recommendation (17Jun2022)	5.2.3 Exclusion criteria specific to Part B, 5.2.5 Exclusion criteria specific to Part D
32	A note was added specifying that nivolumab is to be used as per the approved label in the respective country	Revised according to the ANSM's request/ recommendation (28Mar2022)	6.1.2.1 mFOLFOX6 and nivolumab
33	Clarification was added that treatment is to be discontinued in case a patient develops a DLT, unless the patient has a demonstrable clinical benefit from treatment at the same time	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMP's recommendation (11 May 2022)	6.5.1 Dose modification and toxicity management for SOT102

Change number	Description of change	Rationale for change	Section in Amendment 2
34	Information was added that caution should be exercised when administering trial medication with medications known as substrates of CYP2D6 and CYP3A, when administering trial medication or nab-paclitaxel with QT/QTc interval-prolonging medications; recommendation against use of CYP2C8 and CYP3A4 inducers added for EU in cohorts including nab-paclitaxel	Revised according to the ANSM's request/ recommendation (28Mar2022), AFMPS's request/recommendation (11May2022), and AFMPS's request/ recommendation (06Apr2022)	6.8.3 Medications requiring special caution; 6.8.3.2 Nab-paclitaxel
35	Clarification was added of the timing of radiology assessments throughout the trial	Revised for better clarity	8.1.1 Radiologic evaluation of disease
36	ECOG collection moved from section on efficacy measures (8.1.2) to section on safety (8.2.1)	Revised for better clarity	8.2.1 Physical examinations, body height, weight, and surface area, ECOG performance status
37	In the event of grade ≥3 corrected QT/QTc interval prolongation, continuous monitoring of ECG is recommended	Revised according to the ANSM's request/ recommendation (28Mar2022) and AFMPS's request/recommendation (06Apr2022)	8.2.4 Electrocardiography
38	Clarification was added to specify the communication between the sponsor and investigators regarding SUSARs	Revised according to the ANSM's request/ recommendation (28Mar2022)	8.3.5 Regulatory reporting requirements for SAEs
39	Information on what needs to be documented in eCRF on AE page specified (Other suspected cause and Other action taken are not to be recorded)	Revised for better clarity	8.3.8.2 Documenting in eCRFs
40	Clarification was added that both efficacy and safety data will be reviewed by the IDMC in Part C and Part D	Revised according to the ANSM's request/ recommendation (28Mar2022)	10.1.11 Independent data monitoring committee
41	Clarification on sponsor's contractors being excluded from third parties added	Revised for better clarity	10.1.12 Future research
42	List of CYP2D6 and/or CYP3A substrates included in list of medications requiring special caution	Revised according to the AFMPS's request/ recommendation (06Apr2022)	10.5 Appendix 5: List of medications requiring special caution
43	Change of Statistician	Change of personnel	SIGNATURES/PROTOCOL APPROVAL AND RELEASE SOTIO
44	Minor wording and punctuation corrections	To improve clarity and readability	Throughout the document

10.7.5 Amendment FR-2 (22Jun2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment FR-2
1	Footnotes 5 and 10 of the schedules of activities for Part A and Part B were clarified as follows (addition underlined): "5. Before SOT102 administration in each cycle" "10. Within 15 minutes after the end of SOT102 infusion in each cycle; additionally, 24 hours after the end of SOT102 infusion in cycle 1 and cycle 3"	Revised according to the ANSM's request/recommendation (17Jun2022): *Due to the risk of QTc interval prolongation observed during preclinical studies with SOT102 but also because this is a first in human study, Sponsor is asked to modify the protocol, so as to perform a triple ECG at T0 (baseline), Tmax (D1) and at steady state (at least 5 product half-lives) regularly during part A and B and not as clinically indicated or only at cycle 1 and 3 as indicated in the resubmission. It should be done, at least Q3W during all escalation parts and could be adapted for expansion parts.*	Sections 1.3.1 Schedule of activities, Part A (SOT102 monotherapy, dose escalation, CLDN18.2-agnostic), 1.3.2 Schedule of activities, Part B gastric (SOT102 combination with first-line SoC treatment, dose escalation, CLDN18.2-agnostic), 1.3.3 Schedule of activities, Part B pancreatic (SOT102 combination with first-line SoC treatment, dose escalation, CLDN18.2-agnostic)
2	The list of exceptions from DLTs in protocol section 4.1.1.1 was modified as follows (addition underlined): "Grade 3 or higher amylase or lipase not associated with symptoms or clinical manifestations or radiological evidence of pancreatitis"	Revised according to the ANSM's request/recommendation (17Jun2022): *Sponsor is asked to modify section 4.1.1.1 (Dose-Limiting Toxicities definitions) so as the DLT exception will be "≥ grade 3 amylase or lipase that is not associated with symptoms, or clinical manifestations, or radiological imaging of pancreatitis". Indeed, clinical symptoms are not sufficient to detect pancreatitis, imaging is needed when there is grade 3 amylase or lipase to exclude pancreatitis. The Sponsor has not provided a satisfactory response to this point. This is a FIH and a pancreatic toxicity cannot be ruled out and as already stated, an imagery is mandatory in case of grade 3 amylase or lipase increase.*	Section 4.1.1.1 Dose-limiting toxicities definitions
3	Section 5.2.1 Exclusion criteria applicable to all trial parts was modified as follows (addition underlined): "Patient has been previously treated with the maximum cumulative dose of anthracyclines"	Revised according to the ANSM's request/recommendation (17Jun2022): *Concerning exclusion criteria, Sponsor is asked to modify the protocol so as to exclude patient previously treated with anthracyclines at the maximum cumulative dose.*	Section 5.2.1 Exclusion criteria applicable to all trial parts

Change number	Description of change	Rationale for change	Section in Amendment FR-2
4	Sections 5.2.3 with exclusion criteria specific to Part B and 5.2.5 with exclusion criteria specific to Part D were amended as follows (addition underlined): "Patients more clinically suitable (e.g., with BRCA1/2 mutation) to receive treatment with leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin (FOLFIRINOX) as compared to nab-paclitaxel and gemcitabine according to the investigator's opinion"	Revised according to the ANSM's request/recommendation (17Jun2022): *Sponsor is asked to modify the inclusion criteria so as not to authorise the inclusion of patients with pancreatic adenocarcinoma in part B and D eligible for FOLFIRINOX:* *• per Investigator's opinion. Indeed, a patient may be more clinically suitable to receive FOLFIRINOX than nab-paclitaxel and gemcitabine according to the investigator.* *• and also because patients with BRCA1/2 mutation will be more sensitive to platinum based chemotherapy and so to FOLFIRINOX as according to ESMO guidelines* *This two points must be outlined in the protocol.*	Sections 5.2.3 Exclusion criteria specific to Part B, 5.2.5 Exclusion criteria specific to Part D

10.7.6 Amendment BE-2 (26May2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment BE-2
1	Stopping rules were moved from section 4.1.1.7 to section 5.5 and were updated to include all trial parts and all cohorts. Section 4.1.1.7 was removed.	Revised according to the AFMP's recommendation (11 May 2022): *R1: The Applicant is recommended to include a separate section in the protocol with more specific guidance to investigator for the purpose of management of treatment-emergent toxicities. This section could list actions toward investigational medication (eg dose reductions, temporary/permanent discontinuation), additional examinations/labs/imaging or potential treatments/referral to specialist*	5.5 Criteria for temporarily delaying enrollment/ administration of trial intervention
2	Clarification was added that treatment is to be discontinued in case a patient develops a DLT, unless the patient has a demonstrable clinical benefit from treatment at the same time	Revised according to the AFMP's recommendation (11May 2022): *R1: The Applicant is recommended to include a separate section in the protocol with more specific guidance to investigator for the purpose of management of treatment-emergent toxicities. This section could list actions toward investigational medication (eg dose reductions, temporary/permanent discontinuation), additional examinations/labs/imaging or potential treatments/referral to specialist*	6.5.1 Dose modification and toxicity management for SOT102

Change number	Description of change	Rationale for change	Section in Amendment BE-2
3	Information was added that caution should be exercised when administering trial medication medications known as substrates of CYP2D6 and CYP3A	Revised according to the AFMP's recommendation (11May 2022): *R3: The applicant is asked to include CYP2D6 and CYP3A substrates in section 6.8.3 Medications requiring special caution of the protocol*	6.8.3 Medications requiring special caution
4	Information was added that caution should be exercised when administering trial medication with QT/QTc interval-prolonging medications	Revised according to the AFMPS's request/recommendation (11May2022): *C1: Considering the potential for QT prolongation identified for SOT102 in the safety pharmacology study in cynomolgus monkeys and the absence of a GLP hERG assay. Concomitant therapies with a potential for QT prolongation should be used with caution or prohibited in all parts of the trial until the QT prolongation potential of SOT102 is further characterized. The relevant wording should be included in the protocol.*	6.8.3 Medications requiring special caution

10.7.7 Amendment BE-1 (03May2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment BE-1
1	Monitoring of SaO_2 was added to the assessments to be performed in the trial for all trial parts and all cohorts	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 7: In the primary PD section, CLDN18.2 expression was seen in lung xenograft models and microscopic findings were seen in the rat repeat dose studies indicating a potential for on target effect in the lungs. In addition some of the SOC therapies are associated with a potential for lung/ respiratory AE. The applicant is asked to include specific monitoring in the protocol to detect early lung adverse events as well as management guidelines (clear cut-off value to trigger study drug discontinuation, the timing and frequency of follow-up assessments to monitor after an abnormal result and conditions needed to restart treatment) for all parts of the trial.*	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D)
2	Monitoring of LVEF schedule for Part B was aligned with that of Part A. Monitoring of LVEF was added to the assessments to be performed at 30 (±5) days after the last dose	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 2: The stomach, liver, kidney have been identified as potential target organs for SOT102 toxicity, and non-adverse prolonged QT interval was seen in monkeys. These toxicities also overlap with the potential AE of*	1.3.2 – 1.3.6 Schedule of activities (Part B, Part C, Part D)

Change number	Description of change	Rationale for change	Section in Amendment BE-1
	of SOT102 for trial Part B, Part C, and Part D, all cohorts	*the standard of care therapies. The applicant should thoroughly justify the rationale for the reduced monitoring frequency in part B and D pancreatic cohort. Especially in part B given this will be the first administration of SOT102 with SOC therapies. Safety monitoring including physical exams, vital signs (before, during, after end of infusion), biochemistry, urinalysis, creatinine clearance, ECG (around T max) should be conducted at least at each SOT102 administration (every 14 days,) similarly to the gastric cohorts. In addition, LVEF currently only monitored in part A should be added to the part B, C and D or its absence thoroughly justified.*	
3	Schedule of pregnancy testing during the trial was clarified in Part B pancreatic and Part D pancreatic	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 8: In accordance with the "Recommendations related to contraception and pregnancy testing in clinical trials" of the Clinical trial facilitation group (CTFG) available at the HMA website: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf, the applicant is asked to implement monthly pregnancy testing until the expected end of exposure (5 half-lives) + 6 months. In addition due to the potential of SOT102 to affect male reproductive organs, the applicant is asked to include a recommendation for sperm preservation for patients wishing to become a father in the protocol.*	1.3.3 Schedule of activities (Part B pancreatic), 1.3.6 Schedule of activities (Part D pancreatic)
4	Schedule of physical exams, vital signs, biochemistry, urinalysis, creatinine clearance, and ECG determinations was clarified in Part B pancreatic and Part D pancreatic	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 2: The stomach, liver, kidney have been identified as potential target organs for SOT102 toxicity, and non-adverse prolonged QT interval was seen in monkeys. These toxicities also overlap with the potential AE of the standard of care therapies. The applicant should thoroughly justify the rationale for the reduced monitoring frequency in part B and D pancreatic cohort. Especially in part B given this will be the first administration of SOT102 with SOC therapies. Safety monitoring including physical exams, vital signs (before, during, after end of infusion), biochemistry, urinalysis, creatinine clearance, ECG (around T max) should be conducted at least at each SOT102 administration (every 14 days,) similarly to the gastric*	1.3.3 Schedule of activities (Part B pancreatic), 1.3.6 Schedule of activities (Part D pancreatic)

Change number	Description of change	Rationale for change	Section in Amendment BE-1
		cohorts. In addition, LVEF currently only monitored in part A should be added to the part B, C and D or its absence thoroughly justified.	
5	In the event of grade ≥3 corrected QT/QTc interval prolongation, continuous monitoring of ECG is recommended	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 4: In the protocol the fact that "Concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the trial." is only listed in relation to mFOLFOX6 and in the appendix 5 concerned drugs appear under the list of medications requiring special cautions. Considering the potential for QT prolongation identified in the safety pharmacology study, drugs with a potential for QT prolongation should be prohibited for the entire trial. The applicant is asked to modify the protocol and appendix 5 accordingly.*	4.1.1.1 Dose-limiting toxicities definitions
6	Discontinuation from therapy mandated for patients who develop toxicities qualified as DLTs	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 1: As this is a FIH trial for SOT102 (IgG1 based) and considering that nivolumab has also been associated with some infusion related reactions, the applicant is asked to include in the protocol management guidelines and stopping rules for infusion related reactions and cytokine release syndrome, in addition the length of patient observation after the end of infusion in each part should be clearly stated and justified*	4.1.1.1 Dose-limiting toxicities definitions
7	Inclusion criterion 3.7 on serum concentrations of potassium, magnesium, and calcium within normal range was added	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 4: In the protocol the fact that "Concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the trial." is only listed in relation to mFOLFOX6 and in the appendix 5 concerned drugs appear under the list of medications requiring special cautions. Considering the potential for QT prolongation identified in the safety pharmacology study, drugs with a potential for QT prolongation should be prohibited for the entire trial. The applicant is asked to modify the protocol and appendix 5 accordingly.*	5.1.1 Inclusion criteria applicable to all trial parts

Change number	Description of change	Rationale for change	Section in Amendment BE-1
8	Exclusion criterion 14 was added to exclude patients with bradycardia from the trial	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 4: In the protocol the fact that "Concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the trial." is only listed in relation to mFOLFOX6 and in the appendix 5 concerned drugs appear under the list of medications requiring special cautions. Considering the potential for QT prolongation identified in the safety pharmacology study, drugs with a potential for QT prolongation should be prohibited for the entire trial. The applicant is asked to modify the protocol and appendix 5 accordingly.*	5.2.1 Exclusion criteria applicable to all trial parts
9	Exclusion criterion 15 was added to exclude patients with family history of sudden cardiac death before age 50 from the trial	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 4: In the protocol the fact that "Concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the trial." is only listed in relation to mFOLFOX6 and in the appendix 5 concerned drugs appear under the list of medications requiring special cautions. Considering the potential for QT prolongation identified in the safety pharmacology study, drugs with a potential for QT prolongation should be prohibited for the entire trial. The applicant is asked to modify the protocol and appendix 5 accordingly.*	5.2.1 Exclusion criteria applicable to all trial parts
10	Exclusion criterion 22 was added for Part B and Part D gastric cohorts to exclude use of medications known to prolong QT/QTc interval during the trial	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 4: In the protocol the fact that "Concomitant use of drugs known to prolong the QT/QTc interval is prohibited during the trial." is only listed in relation to mFOLFOX6 and in the appendix 5 concerned drugs appear under the list of medications requiring special cautions. Considering the potential for QT prolongation identified in the safety pharmacology study, drugs with a potential for QT prolongation should be prohibited for the entire trial. The applicant is asked to modify the protocol and appendix 5 accordingly.*	5.2.3 Exclusion criteria specific to Part B (gastric); 5.2.5 Exclusion criteria specific to Part D (gastric)

Change number	Description of change	Rationale for change	Section in Amendment BE-1
11	Recommendation against use of CYP2C8 and CYP3A4 inducers added for cohorts including nab-paclitaxel	Revised according to the AFMPS's request/recommendation (06Apr2022): *Question 5: The applicant is asked to modify the protocol to clarify that CYP2C8 et CYP3A4 inducers are not recommended instead of authorized with caution in cohorts including nab-paclitaxel.*	6.8.3.2 Nab-paclitaxel
12	List of CYP2D6 and/or CYP3A substrates included in list of medications requiring special caution	Revised according to the AFMPS's request/recommendation (06Apr2022): *Recommendation 2: The applicant is asked to include CYP2D6 and CYP3A4 substrates to the concomitant therapies to use with caution as these may be inhibited by* [redacted]	10.5 Appendix 5: List of medications requiring special caution
13	Change of Statistician	Change of personnel	SIGNATURES/ PROTOCOL APPROVAL AND RELEASE SOTIO

10.7.8 Amendment FR-1 (26Apr2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment FR-1
1	A note was added to the trial design schema to clarify the patient population in Part B and Part D of the trial. In addition, exclusion criterion 17 for Part B and Part D was updated to clarify the same	Revised according to the ANSM's request/recommendation (28Mar2022): *3.11 Sponsor is asked to modify the protocol in order to clarify the lines of therapy required prior enrollments into Parts B and D in inclusion criteria as already requested by FDA, this not clear. According to the schema of design, patient should not have prior therapies in metastatic setting.*	1.2 Schema; 5.2.3 Exclusion criteria specific to Part B; 5.2.5 Exclusion criteria specific to Part D
2	Monitoring of SaO_2 was added to the assessments to be performed in the trial for all trial parts and all cohorts	Revised according to the ANSM's request/recommendation (28Mar2022): *3.8 Concerning monitoring of patient, considering that this is a first in human trial and safety of patient must be the priority, Sponsor is asked to: Add a monitoring of SaO2 for all parts as pulmonary toxicities have been shown in preclinical studies and are expected with standard of care*	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D)

Change number	Description of change	Rationale for change	Section in Amendment FR-1
3	Monitoring of HIV and HBV for HIV and/or HBV-positive patients was added to the assessments to be performed in the trial for all trial parts and all cohorts	Revised according to the ANSM's request/recommendation (28Mar2022): *3.8 Concerning monitoring of patient, considering that this is a first in human trial and safety of patient must be the priority, Sponsor is asked to: Add monitoring of HBV and HIV serology as clinically indicated as patients with history of such infections can be included and risk of reactivation cannot be escluded*	1.3.1 – 1.3.6 Schedule of activities (Part A, Part B, Part C, Part D); 10.4.3 Clinical chemistry
4	Monitoring of AEs considered as having a suspected causal relationship to SOT102 per the investigator's judgment and monitoring of concomitant medication was added to the follow-up until disease progression or start of new anticancer therapy in Part A and Part B	Revised according to the ANSM's request/recommendation (28Mar2022): *3.8 Concerning monitoring of patient, considering that this is a first in human trial and safety of patient must be the priority, Sponsor is asked to: extend the period of data collection of AE/SAE related to treatment at follow up every 6 weeks and not only at 30 days post-EOT. Indeed considering the half-life of the product and the potential risk of delayed toxicities, the follow-up period of AE monitoring is not appropriate. If necessary, this long-term safety follow-up may be planned as a phone call visit to avoid additional hospital visit and burden for patients who might be followed in another site after study treatment discontinuation. Survival and concomitant therapies should also be followed in part A and B*	1.3.1 – 1.3.3 Schedule of activities (Part A, Part B); 4.1.2.4 Follow-up period (Part A); 4.1.3.4 Follow-up period (Part B); 8.3.2 Time period and frequency for collecting AE, SAE, and other reportable safety event information
5	Monitoring of LVEF schedule for Part B was aligned with that of Part A	Revised according to the ANSM's request/recommendation (28Mar2022): *3.8 Concerning monitoring of patient, considering that this is a first in human trial and safety of patient must be the priority, Sponsor is asked to: add a monitoring of LVEF every 2 cycles for part B as it is planned for part A. Indeed, combinations has never been tested in a clinical setting, and cardiac toxicity related to anthracyclin cannot be excluded.*	1.3.2, 1.3.3 Schedule of activities (Part B gastric, Part B pancreatic)
6	Monitoring of LVEF was added to the assessments to be performed at 30 (±5) days after the last dose of SOT102 for trial Part B, Part C, and Part D, all cohorts	Revised according to the ANSM's request/recommendation (28Mar2022): *3.8 Concerning monitoring of patient, considering that this is a first in human trial and safety of patient must be the priority, Sponsor is asked to: Add an end of treatment visit during which most of the parameters followed during treatment will be assess (coagulation, vital signs, physical examination, biochemistry, hematology, urinalysis, creatinine clearance, AE, LVEF)*	1.3.2 – 1.3.6 Schedule of activities (Part B, Part C, Part D)

Change number	Description of change	Rationale for change	Section in Amendment FR-1
7	Number of patients to be treated at the RP2D before opening expansion cohorts was clarified	Revised according to the ANSM's request/recommendation (28Mar2022): *3.10 Sponsor is asked to clarify in the protocol that at least 6 patients evaluable for DLT will be treated at the RP2D before opening expansion parts as also requested by FDA (for both part A and B). Indeed, the wording is not clear in the protocol*	4.1.1 Dose escalation plan (Part A and Part B); 4.1.1.2 Maximum tolerated dose and selection of the recommended phase 2 dose; 9.5.1 Part A (SOT102 monotherapy, dose escalation); 9.5.2 Part B (SOT102 combined with first-line SoC treatment, dose escalation)
8	In the event of grade ≥3 corrected QT/QTc interval prolongation, continuous monitoring of ECG is recommended	Revised according to the ANSM's request/recommendation (28Mar2022): *3.5 Sponsor is asked to modify the protocol, due to the risk of QTc interval prolongation observed during preclinical studies with SOT102 but also because this is a first in human study and combinations have never been tested in preclinical studies so safety of monotherapy and combinations is not known: so as to provide for the following in the event of QT/QTc interval prolongation greater than 500 ms (grade 3 toxicity): initiation of close and appropriate ECG monitoring (continuously) in hospital until a cardiologist's opinion is issued*	4.1.1.1 Dose-limiting toxicities definitions
9	Communication plan between the sponsor, the investigators, and the subjects in the event of emerging safety issues was updated	Revised according to the ANSM's request/recommendation (28Mar2022): *3.16 The sponsor is asked to modify the protocol so as to describe: the communication plan between the sponsor, the investigators and the subjects participating in the trial, in the event of emerging safety issues*	4.1.1.6 Communication plan
10	Stopping rules were moved from section 4.1.1.7 to section 5.5 and were updated to include all trial parts and all cohorts. Section 4.1.1.7 was removed.	Revised according to the ANSM's request/recommendation (28Mar2022): *3.6 Sponsor must define in the protocol unambiguous safety stopping rules for expansion parts and entire study that result in discontinuation of enrollment in case of unexpected toxicity signal observed. This demand is in accordance with the GCP applicable to all clinical trials regardless of the development phase (ICH E6, section 6.4: "A description of the trial design, should include [...] A description of the stopping rules or discontinuation criteria for individual subjects, parts of trial and entire trial") and the recommendations of the "guideline on strategies to identify and mitigate*	5.5 Criteria for temporarily delaying enrollment/administration of trial intervention

Change number	Description of change	Rationale for change	Section in Amendment FR-1
		risks for first-in-human and early clinical trials with investigational medicinal products" (section 8.2.9). *Stopping rules criteria must be based on safety parameters such as the frequency and severity of adverse events and these parameters must be specified in the protocol. These rules a priori will be followed by the safety committee to take the temporary stopping decisions before final decision (e.g. permanent discontinuation, dose reduction of a treatment in the combination or adaptation of the monitoring plan). The rules may be applied for each cohorts in a way to be able to continue some cohorts while others are stopped.*	
11	Inclusion criterion 3.7 on serum concentrations of potassium, magnesium, and calcium within normal range was added	Revised according to the ANSM's request/recommendation (28Mar2022): *3.4 Concerning exclusion criteria, as this is a FIH trial and some patients will be treated in first line, Sponsor is asked to modify the protocol so as to: Exclude patient with marked and persistent bone marrow depression and/or severe stomatitis induced by previous cytotoxic and/or radiotherapy treatment (including in patients at high risk of bleeding), acute inflammatory heart disease, previous treatment with an anthracycline at the maximum cumulative dose and hypersensitivity to anthracycline*	5.1.1 Inclusion criteria applicable to all trial parts
12	Inclusion criterion 6.2 was modified to specify that a highly effective contraceptive method must be used during the treatment period and for at least 9 months after the last dose of SOT102 or first-line SoC treatment (whichever occurs later).	Revised according to the ANSM's request/recommendation (28Mar2022): *3.9 Concerning the contraception, in accordance with the recommendations of the CTFG regarding pregnancy risk management (Recommendations related to contraception and pregnancy testing in clinical trials), Sponsor is asked to modify the protocol in order to: Take in account duration of contraception according to each chemotherapies and nivolumab in case that the last drug administered is not SOT102*	5.1.1 Inclusion criteria applicable to all trial parts
13	Inclusion criterion 7 was modified to specify that a highly effective contraceptive method must be used by WOCBP partners of male participants	Revised according to the ANSM's request/recommendation (28Mar2022): *3.9 Concerning the contraception, in accordance with the recommendations of the CTFG regarding pregnancy risk management (Recommendations related to contraception and pregnancy testing in clinical trials), Sponsor is asked to modify the protocol in order to: Take in account duration of*	5.1.1 Inclusion criteria applicable to all trial parts

Change number	Description of change	Rationale for change	Section in Amendment FR-1
		contraception according to each chemotherapies and nivolumab in case that the last drug administered is not SOT102	
14	Exclusion criterion 7 was updated to specify that an active infection must be clinically controlled before patient's inclusion in the trial	Revised according to the ANSM's request/recommendation (28Mar2022): *3.4 Concerning exclusion criteria, as this is a FIH trial and some patients will be treated in first line, Sponsor is asked to modify the protocol so as to: Modify exclusion criteria 7 by specifying that infection must be controlled with antibiotics before inclusion*	5.2.1 Exclusion criteria applicable to all trial parts
15	Exclusion criterion 11 was updated to specify that patients with NYHA ≥2 heart failure must be excluded from the trial	Revised according to the ANSM's request/recommendation (28Mar2022): *3.4 Concerning exclusion criteria, as this is a FIH trial and some patients will be treated in first line, Sponsor is asked to modify the protocol so as to: Modify exclusion criteria 11 in order to exclude patient with NYHA≥2 heart failure, this a FIH trial with a product in monotherapy or in combination with expected cardiac toxicities*	5.2.1 Exclusion criteria applicable to all trial parts
16	Exclusion criterion 14 was added to exclude patients with bradycardia from the trial	Revised according to the ANSM's request/recommendation (28Mar2022): *3.5 Sponsor is asked to modify the protocol, due to the risk of QTc interval prolongation observed during preclinical studies with SOT102 but also because this is a first in human study and combinations have never been tested in preclinical studies so safety of monotherapy and combinations is not known: so as not to enable the inclusion of patients who present the following in this trial: bradycardia (< 50 beats per minute)*	5.2.1 Exclusion criteria applicable to all trial parts
17	Exclusion criterion 15 was added to exclude patients with family history of sudden cardiac death before age 50 from the trial	Revised according to the ANSM's request/recommendation (28Mar2022): *3.5 Sponsor is asked to modify the protocol, due to the risk of QTc interval prolongation observed during preclinical studies with SOT102 but also because this is a first in human study and combinations have never been tested in preclinical studies so safety of monotherapy and combinations is not known: so as not to enable the inclusion of patients who present the following in this trial: family history of sudden cardiac death before age 50*	5.2.1 Exclusion criteria applicable to all trial parts

Change number	Description of change	Rationale for change	Section in Amendment FR-1
18	Exclusion criterion 19 was added for Part B and Part D to exclude patients with clinically active inflammatory bowel disease from the trial	Revised according to the ANSM's request/recommendation (28Mar2022): *3.4 Concerning exclusion criteria, as this is a FIH trial and some patients will be treated in first line, Sponsor is asked to modify the protocol so as to: Precise exclusion of patients with IBD*	5.2.3 Exclusion criteria specific to Part B; 5.2.5 Exclusion criteria specific to Part D
19	Exclusion criterion 22 was added for Part B and Part D gastric cohorts to exclude use of medications known to prolong QT/QTc interval during the trial	Revised according to the ANSM's request/recommendation (28Mar2022): *3.4 Concerning exclusion criteria, as this is a FIH trial and some patients will be treated in first line, Sponsor is asked to modify the protocol so as to: Exclude patient with concomitant use of drugs known to prolong QT/QTc interval in association with mFOLFOX6 to be in accordance with section 6.8.3.1*	5.2.3 Exclusion criteria specific to Part B (gastric); 5.2.5 Exclusion criteria specific to Part D (gastric)
20	A note was added specifying that nivolumab is to be used as per the approved label in the respective country	Revised according to the ANSM's request/recommendation (28Mar2022): *3.2 Sponsor is asked to modify the protocol so as to comply with the updated SPC of nivolumab which have the indication in patients with gastric/GEJ adenocarcinoma with PD-L1 CPS ≥ 5, this parameter must be specify in inclusion criteria*	6.1.2.1 mFOLFOX6 and nivolumab
21	Clarification was added that treatment is to be discontinued in case a patient develops a DLT, unless the patient has a demonstrable clinical benefit from treatment at the same time	Revised according to the ANSM's request/recommendation (28Mar2022): *3.14 Sponsor is asked to modify in the protocol so as to clarify that occurrence of a DLT will lead to treatment discontinuation as no dose reduction or treatment delay are allowed in part A and B in the first two cycles according to section 6.5.1*	6.5.1 Dose modification and toxicity management for SOT102
22	Information was added that caution should be exercised when administering trial medication or nab-paclitaxel with QT/QTc interval-prolonging medications	Revised according to the ANSM's request/recommendation (28Mar2022): *3.5 Sponsor is asked to modify the protocol, due to the risk of QTc interval prolongation observed during preclinical studies with SOT102 but also because this is a first in human study and combinations have never been tested in preclinical studies so safety of monotherapy and combinations is not known: so as to mention in the concomitant treatments section that drugs known to cause QTc interval prolongation must be used with precaution for all part except in gastric cohorts since they are prohibited*	6.8.3 Medications requiring special caution; 6.8.3.2 Nab-paclitaxel

Change number	Description of change	Rationale for change	Section in Amendment FR-1
23	Clarification was added to specify the communication between the sponsor and investigators regarding SUSARs	Revised according to the ANSM's request/recommendation (28Mar2022): *3.16 The sponsor is asked to modify the protocol so as to describe: the plan for rapid communication of suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients in accordance with the "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" section 8.2.10*	8.3.5 Regulatory reporting requirements for SAEs
24	Clarification was added that both efficacy and safety data will be reviewed by the IDMC in Part C and Part D	Revised according to the ANSM's request/recommendation (28Mar2022): *3.17 Sponsor is asked to add an interim analysis including efficacy parameters in order to be able to stop the study in case of lack of efficacy in accordance with "Guideline for good clinical practice E6" section 1.32 and 5.4.1. This is highly recommended especially since this is a multicentre FIH trial.*	10.1.11 Independent data monitoring committee
25	Change of Statistician	Change of personnel	SIGNATURES/ PROTOCOL APPROVAL AND RELEASE SOTIO

10.7.9 Amendment CZ-1 (01Mar2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment CZ-1
1	Addition of exclusion criterion no. 16 for all trial parts	Revised according to the SUKL's recommendation (SUKL RFI 11Feb2022): *We require that you add to the exclusion criteria that patients who would be vaccinated with a live vaccine 30 days prior to the administration of the 1st dose, then during and 90 days after the end of the CT, may not be enrolled.*	Section 5.2.1 Exclusion criteria applicable to all trial parts

Change number	Description of change	Rationale for change	Section in Amendment CZ-1
2	Change of Statistician	Change of personnel	SIGNATURES/ PROTOCOL APPROVAL AND RELEASE SOTIO

10.7.10 Amendment 1 (14Jan2022): Protocol changes implemented

Change number	Description of change	Rationale for change	Section in Amendment 1
1	PK sampling schedule revised to include separate sampling schedule for Part C and Part D	Revised according to the FDA's recommendation (FDA RFI 12Jan2022): *Specific pharmacokinetic (PK) sampling time points in Part C and D. The sparse PK sampling collected in Part C and D should allow for population PK and exposure-response analyses to facilitate SOT102 dose selection. The PK sampling time points should include C_{max} after the first dose as well as C_{max} and C_{trough} at steady state.*	Section 1.3.8 PK and ADA sampling (SOT102) for Part C and Part D; sections 1.3.4 – 1.3.6 Schedule of activities Part C, Part D gastric, Part D pancreatic
2	PK analysis plan revised to include all analytes as listed in Objectives.	Revised according to the FDA's recommendation (FDA RFI 12Jan2022): *Revise the protocol to include total SOT102, conjugated SOT102, [redacted] in the PK analysis plan (Page 77).*	Section 8.4 Pharmacokinetics
3	Warning about use of medications that are known inhibitors or inducers of CYP3A4 or CYP2C9 for Part A and Part B added.	Revised based on the FDA's recommendation (FDA RFI 12Jan2022): *Avoid concomitant use of medications that are known inhibitors or inducers of CYP3A4 or CYP2C9 in Part A and B to minimize any potential effect on [redacted] and [redacted]-linker containing metabolites exposure. Revise the protocol to monitor adverse events closely when administering SOT102 with medications that are known inhibitors or inducers of CYP3A4 or CYP2C9 in Part C and D.*	Section 6.8.3 Medications requiring special caution; section 10.5 List of medications requiring special caution

Change number	Description of change	Rationale for change	Section in Amendment 1
4	ECG measurement schedule clarified for Part A and Part B. Possible revision of ECG measurement schedule added for Part C and Part D.	Revised based on the FDA's recommendation (FDA RFI 12Jan2022): *Collect ECG at baseline (screening), pre-dose and around time of maximum drug concentration (T_{max}) after the first dose and at steady state, periodically during the study, and as clinically indicated in Part A and B. Revise the protocol to re-evaluate the ECG collection plan in Part C and D with the emerging data form Part A and B.*	Section 8.2.4 Electrocardiography sections 1.3.1 – 1.3.3 Schedule of activities Part A, Part B gastric, Part B pancreatic
5	Inclusion criterion no. 15 revised for clarity	Revised based on the FDA's recommendation (FDA RFI 13Jan2022): *Inclusion criteria #15 is unclear and may be subjectively interpreted. Modify this inclusion criterion to state: Patient has received and/or has been determined to be intolerant of all standard of care therapy known to confer clinical benefit.*	Section 1.1 Synopsis; Section 5.1.2 Inclusion criteria specific to Part A
6	Definition of what constitutes an exception to DLTs was modified	Revised based on the FDA's recommendation (FDA RFI 13Jan2022): *The following is not an acceptable DLT exception and should be removed:* *a. Grade 3 aspartate transaminase (AST) or alanine transaminase (ALT) or grade 3 bilirubinemia that lasts ≤5 days*	Section 4.1.1.1 Dose-limiting toxicities definitions
7	Dose modification and toxicity management for SOT102 and first-line SoC revised to provide more guidance	Revised based on the FDA's recommendation (FDA RFI 13Jan2022): *Modify the trial to include specific dose modification guidelines for SOT102 based on NCI CTCAE v5.0 grade of observed toxicity. These dose modification guidelines should include the following:* *a. Instructions on when to hold and permanently discontinue study treatment based on toxicity* *i. (i.e. treatment interruptions for Grade 3+ and intolerable or persistent Grade 2 AE that occur after the DLT evaluation period in Parts A and B and for the duration of treatment in Parts C and D)*	Section 6.5.1 Dose modification and toxicity management for SOT102; section 6.5.2 Dose modification and toxicity management for first-line SoC treatment

Change number	Description of change	Rationale for change	Section in Amendment 1
		ii. Permanent discontinuation of study treatment for Grade 4 adverse events *b. Instructions on when study treatment may be restarted (i.e. upon resolution of AE to grade ≤1 or baseline)* *d. Instructions for management of recurrent toxicity* *e. Instructions for managing combination regimen when AE cannot be clearly attributed to one drug in the combination (i.e. recommendations describing which drugs to hold initially in response to AE versus recommendation to hold all drugs in the combination)* *f. Guidelines should include a maximum allowable period (i.e. 2 weeks or 1 cycle) in which toxicity must resolve before study treatment is discontinued.*	
8	Schedule of patient monitoring clarified in Schedule of activities for Part A	Revised based on the FDA's recommendation (FDA RFI 13Jan2022): *In the schedule of activities listed in 1.3.1 for Part A, the frequency in which patient monitoring (i.e. physical exams, AE assessment) will occur is unclear. Clarify whether patients will receive the assessments listed on both Day 1 and Day 8 of each 14-day cycle or on Day 1 of each cycle only.*	Section 1.3.1 Schedule of activities, Part A
9	Exclusion criterion no. 8 on HIV, hepatitis B, and hepatitis C patients revised to allow their participation under specific circumstances	Revised based on the FDA's recommendation (FDA RFI 13Jan2022): *The FDA generally recommends against blanket exclusion of patients with HIV, Hepatitis B or Hepatitis C on clinical trials. See: FDA Guidance to Industry on Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections (https://www.fda.gov/media/121319/download)*	Section 5.2.1 Exclusion criteria applicable to all trial parts
10	Inclusion criterion no. 13 for Part A and Part C revised to remove time-based washout and recovery period	Revised based on the FDA's recommendation (FDA RFI 13Jan2022): *FDA generally recommends against time-based washout and recovery periods within the eligibility criteria unless scientifically justified. Eligibility should be determined based on patient recovery from clinically significant adverse events from their most recent therapy or intervention*	Section 5.1.2 Inclusion criteria specific to Part A; section 5.1.4 Inclusion criteria specific to Part C

Change number	Description of change	Rationale for change	Section in Amendment 1
		prior to study enrollment. Although not official FDA guidance, you may refer to recent publication from ASCO and FOCR for further rationale (https://clincancerres.aacrjournals.org/content/27/9/2400).	

10.8 Appendix 8: Country-specific requirements/differences

Country	Section(s) in Protocol Amendment 5	Country-specific requirements/differences
France (per country-specific amendment FR-3 dated 01Sep2022)	5.1 Inclusion criteria, criterion 12	All previous cancer therapies for locally advanced pancreatic cancer and any agents that have not received regulatory approval for any indication must have been discontinued **for ≥21 days or ≥5 half-lives, whichever is longer.** Patients must have recovered from the acute effects of therapy and treatment-related toxicities must have reached grade ≤1 (exception: alopecia). Mitomycin-C and nitrosoureas must have been discontinued for ≥42 days.
	10.4.3 Clinical chemistry	**Cholesterol, fibrinogen, and triglycerides** are to be evaluated at screening, prior to each cycle, and at 30 (+5) days after the last dose of SOT102 under fasting conditions.

11 REFERENCES

1. Ferlay J, Ervik M, Colombet M, et al. Global Cancer Observatory: Cancer Today. https://gco.iarc.fr/today/home. Published 2020. Accessed September 01, 2022.
2. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):v38-v49.
3. Ishii T, Kawazoe A, Shitara K. Dawn of precision medicine on gastric cancer. *Int J Clin Oncol.* 2019;24(7):779-788.
4. Prades J, Arnold D, Brunner T, et al. Bratislava Statement: consensus recommendations for improving pancreatic cancer care. *ESMO Open.* 2020;5(6).
5. Wang-Gillam A, Hubner RA, Siveke JT, et al. NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: Final overall survival analysis and characteristics of long-term survivors. *Eur J Cancer.* 2019;108:78-87.
6. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.
7. Hacibekiroglu I, Kodaz H, Erdogan B, et al. Comparative analysis of the efficacy and safety of modified FOLFOX-6 and DCF regimens as first-line treatment in advanced gastric cancer. *Mol Clin Oncol.* 2015;3(5):1160-1164.
8. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *The Lancet.* 2021;398(10294):27-40.
9. Nivolumab SmPC EU. https://www.medicines.org.uk/emc/product/6888/smpc. Accessed September 01, 2022.
10. Dan N, Setua S, Kashyap VK, et al. Antibody-drug conjugates for cancer therapy: Chemistry to clinical implications. *Pharmaceuticals (Basel).* 2018;11(2).
11. Adcetris USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125388s100lbl.pdf. Accessed September 01, 2022.
12. Besponsa USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf. Accessed September 01, 2022.
13. Blenrep USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761158s000lbl.pdf. Accessed September 01, 2022.
14. Enhertu USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761139s011lbl.pdf. Accessed September 01, 2022.
15. Kadcyla USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125427s108lbl.pdf. Accessed September 01, 2022.

16. Padcev USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s007lbl.pdf. Accessed September 01, 2022.

17. Polivy USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761121Orig1s003lbl.pdf. Accessed September 01, 2022.

18. Trodelvy USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761115s009lbl.pdf. Accessed September 01, 2022.

19. Zynlonta USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761196s000lbl.pdf. Accessed September 01, 2022.

20. Mylotarg USPI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf. Accessed September 01, 2022.

21. Osanai M, Takasawa A, Murata M, Sawada N. Claudins in cancer: bench to bedside. *Pflugers Arch.* 2017;469(1):55-67.

22. Sahin U, Koslowski M, Dhaene K, et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. *Clin Cancer Res.* 2008;14(23):7624-7634.

23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

24. Hanauske A-R, Von Hoff DD. Preclinical and Early Clinical Development of Chemotherapeutic Drugs, Mechanism-Based Agents and Biologics. In: *Holland-Frei Cancer Medicine.*2017:573-587.

25. Nivolumab USPI. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed September 01, 2022.

26. Nab-paclitaxel (Abraxane) SmPC EU. https://www.medicines.org.uk/emc/product/6438/smpc#gref. Accessed September 01, 2022.

27. Gemcitabine SmPC EU. https://www.medicines.org.uk/emc/product/7298/smpc#gref. Accessed September 01, 2022.

28. Oxaliplatin SmPC EU. https://www.medicines.org.uk/emc/product/6088/smpc#gref. Accessed September 01, 2022.

29. Leucovorin SmPC EU. https://www.medicines.org.uk/emc/product/6373/smpc. Accessed September 01, 2022.

30. 5-Fluorouracil SmPC EU. https://www.medicines.org.uk/emc/product/6041/smpc. Accessed September 01, 2022.

31. Ferlay J, Ervik M, Colombet M, et al. Global Cancer Observatory: Cancer Today. https://gco.iarc.fr/today/home. Published 2020. Accessed February 28, 2022.

32. International Council for Harmonisation. ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s9-non-clinical-evaluation-anticancer-pharmaceuticals-step-5_en.pdf. Accessed September 01, 2022.

33. International Council for Harmonisation. E6 Good Clinical Practice Guideline. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf. Published 2016. Accessed September 01, 2022.

34. Council of Europe Committee of Ministers. Recommendation CM/Rec (2016)6 of the committee of ministers to member states on research on biological materials of human origin. https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=090000168064e8ff. Published 2016. Accessed September 01, 2022.

35. Meid AD, Bighelli I, Mächler S, et al. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. *Ther Adv Psychopharmacol.* 2017;7(12):251-264.

36. U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Published 2020. Accessed September 01, 2022.