A Phase I/II Open-Label, Three-Part, Dose-Finding and Separate Cohort Expansion Trial to Assess the Safety, Tolerability and Preliminary Efficacy of Repeated Doses of CLEVER-1 Antibody FP-1305, in Subjects with Advanced Solid Tumours

MATINS Study Protocol

Macrophage **A**ntibody **T**o **IN**hibit Immune **S**uppression

Sponsor Study Number:	FP2CLI001
EudraCT Number:	2018-002732-24
IND Number:	144585
Protocol Version:	11
Protocol Date:	22Dec2021

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Serious Adverse Event (SAE) /Adverse Event of Special Interest (AESI)/Dose Limiting Toxicity (DLT) & Delayed Toxicity Reporting

PREFERRED:
Reporting in Electronic Case Report Form (eCRF) Adverse Events page [preferred]

BACK-UP:
Paper SAE/AESI Form [back-up method for SAE/AESI]
Email to Medical Monitor [back-up method for DLT/delayed Toxicity]

Paper SAE Form (back-up method for SAE/AESI)

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Protocol Version: 11, 22Dec2021

This protocol has been approved by:

Name: Dr. [redacted], MD, PhD **Trial Role:** Interim Chief Medical Officer

Signature and Date:

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Protocol Version: 11, 22Dec2021

Name: Dr. [redacted], MD, PhD **Trial Role:** Global Co-ordinating Investigator

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This protocol describes the MATINS trial and provides information about procedures for trial subjects taking part in the trial. The protocol should not be used as a guide for treatment of patients not taking part in the MATINS trial.

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Protocol Version: 11, 22Dec2021

Name: **Trial Role:** Principal Investigator

Signature: **Date:**

_____ _____

Site address: _____

_____

Phone: _____

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AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
01	24Apr2019	04	Substantial	Revision of the eligibility criteria, treatment beyond progression (defined by RECIST 1.1 criteria) and possibility to continue on study treatment beyond one year. Several clarifications in e.g. dose escalation rules, schedule of assessments and AE reporting.
Administrative change (FI)	17Jun2019	04.1	Non-substantial	A typo was corrected on page 54 according to Fimea´s request dated 13Jun2019.
Substantial change (UK)	01Jul2019	04.2	Substantial	Safety monitoring during the second year of treatment and exclusion criterion 6 were defined according to MHRA´s request dated 25Jun2019.
02	20Aug2019	05	Substantial	PK-sampling time-points adjusted. New laboratory tests (endocrine panel) added. New cohorts added for Part II. Trial subject numbers increased for Parts I, II and III. Number of sites amended. Possibility to include sites in the United States added. Possibility to collect and analyse diagnostic sample added. A brain CT-scan procedure added in screening and subjects with brain metastases excluded. A possibility to adjust a dose for first subject with a liver specific cancer for safety reasons. IMP dose adjustment according to the subject's weight clarified. Corticosteroid usage instructed in more detail. Text regarding immune-mediated hepatitis clarified. Possibility for treatment hold for subjects with complete response and rechallenge added. Safety reporting after 28-day follow-up period clarified. Text clarifications and address changes.
Substantial change (US)	20Nov2019	05.1	Substantial	Sections 3.1 (Dose Limiting Toxicity) and 7.9 (Management of Toxicities) were modified according to FDA´s request dated 19Nov2019.
Substantial change (US)	25Nov2019	05.2	Substantial	Section 14.7 (Power Calculations) was modified according to FDA´s request dated 22Nov2019.
03	28Nov2019	06	Substantial	Possibility to add more subjects in Part I of the study by DMC to ensure sufficient data for optimal dose selection for Part II. Adjustment of time-points for research blood samples. PK sample adjustments in Parts I and II. Post treatment tumor biopsy advanced from Cycle 4 to Cycle 2. Mandatory biopsy changed to optional in Part III. Biomarkers for Part II and III were modified/updated. P-PTH measurement added. Definition of time period for collecting concomitant medication. Clarification for assessments and dosing if the treatment for subject with CR is re-initiated. Text clarifications and correction of typos. Restructuring the synopsis format.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
03	28Nov2019, revision 25Feb2020	06	Non-substantial	Wording describing genetic analyses was revised. Research blood sample lines "Monocytes" and "Blood sample for PBMCs isolation" were merged. A typo regarding the PK sampling (Section 8.4.5) and some other typos were corrected.
04	24Jul2020	07	Substantial	Not implemented.
05	15Sep2020	08	Substantial	Anaplastic thyroid cancer cohort added and the estimated number of the subjects revised accordingly based on 10/cohort (at each selected dose level) in Part II and possibility for a cohort to continue to Part III. The first subject with HCC and underlying liver cirrhosis in Part II may be administered one level lower than the recommended dose level for the first dose. Revision of the Data Monitoring Committee responsibilities. ctDNA blood samples added in Parts II and III (applicable only when genetic consent obtained). Laboratory tests for parameters that may be analysed on plasma or serum can be performed according to local practice. Inclusion criterion #3 regarding the tumour sample clarified and tumour sample in Part III changed to optional at the discretion of the Sponsor. Added possibility to utilise tumour samples collected due other reasons (e.g. unscheduled biopsy or another informative sample for clinical reasons) for scientific purpose when available. Tumour imaging at the follow-up visit removed to avoid unnecessary imaging. Objectives and outcome measures clarified. Timeframe set for follow-up period of any reported pregnancy. Separate country specific protocol addendum introduced investigating Q2W and Q1W dosing schemes in selected countries.
06 (Submitted to FI only)	23Apr2021	09	Substantial	New investigated dose levels of 30 mg/kg and 100 mg/kg added. Any dose level below 100 mg/kg may also be tested before escalating the dose to 100 mg/kg. Testing of higher doses (30 and 100 mg/kg) will proceed in parallel with the treatment of other Part II cohorts. HCC subjects may be enrolled to these higher doses only after the safety data of the first 10 subjects on any dose level have been assessed. Exclusion criteria have been revised (3, 4 and 9) and a new exclusion criterion (19) 'Subjects with known hypersensitivity to the IMP or any of the pharmaceutical ingredients' has been added. DW-MRI is no longer done in Part II. New laboratory tests added: troponin for Parts II and III and RO samples (selected sites and cohorts only) in Part II.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				Timepoints for PBMC samples revised. Safety of Covid-19 vaccines addressed in the protocol. Safety reporting related instructions and wording revised and consistency improved. Infusion rates changed; detailed guidance for the infusions on different dose levels provided in Pharmacy Manual.
07	09Jun2021	10	Substantial	Study drug induced liver injury and any new or worsening of existing autoimmunity after the administration of the study drug added as adverse events of special interest. Protocol Addendum investigating Q2W and Q1W dosing will be submitted to all participating countries along with this protocol version.
08	22Dec2021	11	Substantial	The patient cohorts for which DLT and delayed toxicity follow-up applies are clarified. Delayed toxicity follow-up criteria and practices are specified. Assessment of DLTs in Part II dose-escalation subjects is added as primary endpoint to evaluate tolerability of new doses in Part II. New intermediate dose level of 45mg/kg is added to protocol for the Q3W dose escalation (section 4.3) in Part II, as well as de -escalation level of 20 mg/kg. The dose-escalation practices with clear stopping rules are clarified in the protocol for the applicable part II cohorts testing new dosing schemas. For Parts II and III: the frequency of endocrine panel follow-up is increased. Additional time-points for comprehensive metabolic panel are included. For the females with child-bearing potential, monthly pregnancy test (urine/serum) is added (in Q3W every cycle). Additional sCLEVER samples are included. Possibility to obtain biopsy from new lesions is introduced as optional assessment. Time window for Follow-Up visit has been revised for Parts II and III. For clarity the entire Hy's criteria has been written to AESI, and not just referring to Hy's Law Description of the re-screen process has been added in the protocol. Composition of the Data Monitoring Committee has been revised.

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

ABBREVIATIONS

5-FU	5-fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
AFP	Alpha fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anaplastic thyroid cancer
AUC	Area under the curve
BCLC	Barcelona Clinic Liver Cancer
BRCA	Breast cancer gene
CA	Cancer antigen
CBC	Complete blood count
CBR	Clinical benefit rate (CR, PR or SD by RECIST 1.1)
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CK	Creatine kinase
CLEVER-1	Common lymphatic endothelial and vascular endothelial receptor-1
Cmax	Maximum serum concentration of a drug
Cmin	Minimum serum concentration of a drug
CMP	Comprehensive metabolic panel
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRC	Colorectal adenocarcinoma
CRP	C-reactive protein
CSF1R	Colony Stimulating Factor 1 Receptor
CT	Computerized tomography
ctDNA	Circulating tumour deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte antigen-4
D	Day
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen receptor
GCP	Good clinical practice
GE	Gastro-esophageal
h	Hour

HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IMP	Investigational medicinal product
irORR	Immune-related objective response rate
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intra-uterine device
I.V.	Intravenous
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
M1	Pro-inflammatory macrophage
M2	Immunosuppressive macrophage
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
MoA	Mode of action
mmol	Millimole
MRC	Mannose receptor
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OxLDL	Oxidized LDL
OC	Ovarian cancer
ORR	Objective response rate (CR or PR by RECIST 1.1)
PD	Pharmacodynamic
PD-1	Programmed cell death protein-1
PDAC	Pancreatic ductal adenocarcinoma
PK	Pharmacokinetic
PARP	Poly (ADP-ribose) polymerase
PR	Partial response
PTH	Parathyroid hormone
Q3W	Every three weeks
Q2W	Every two weeks
Q1W	Every one week
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
sCLEVER-1	Soluble CLEVER-1
SD	Stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAM	Tumour associated macrophage

TITE-CRM	Time-to-event continual reassessment method
TME	Tumour microenvironment
ULN	Upper Limit of Normal

1 PROTOCOL SUMMARY

1.1 Synopsis

Title:	A Phase I/II Open-Label, Three-Part, Dose-Finding and Separate Cohort Expansion Trial to Assess the Safety, Tolerability and Preliminary Efficacy of Repeated Doses of CLEVER-1 Antibody FP-1305, in Subjects with Advanced Solid Tumours
Study description:	It is hypothesised that by blocking common lymphatic endothelial and vascular endothelial receptor-1 (CLEVER-1) protein with FP-1305 the immune system is reactivated to eradicate tumour cells. This is a first in human study to test the safety, tolerability and preliminary efficacy of FP-1305 in advanced solid tumours. The study is run in three parts. Part I will escalate the dose at pre-determined dose levels to determine the maximum tolerated dose (MTD). Part II will test the selected dose(s) from Part I and may explore new doses in distinct cohorts of predefined tumour types. Part III will expand the Part II cohorts demonstrating efficacy signal.
Objectives:	<u>Primary objectives:</u> **Part I** • To determine the safety, tolerability and recommended dose of FP-1305 for Part II and III in subjects with advanced (inoperable or metastatic) hepatobiliary, pancreatic, colorectal or ovarian cancer or melanoma subjects without standard treatment options **Part II** • To determine the safety, tolerability and preliminary efficacy of FP-1305 monotherapy with the objective response rate (ORR), clinical benefit rate (CBR) and immune-related ORR (irORR) in distinct expansion groups of subjects with advanced (inoperable or metastatic) solid tumours of the selected tumour types **Part III** • To assess the ORR, CBR and irORR in distinct expansion groups of subjects with advanced solid tumours in CLEVER-1 positive subjects from selected tumour types at a selected dose <u>Secondary objectives:</u> **Part I** • To characterize the pharmacokinetic (PK) profile of a single dose of FP-1305 after the first dosing • To characterize the PK profile of FP-1305 during repeated dosing • To assess the host immune response to FP-1305 (immunogenicity) • To assess the preliminary efficacy of FP-1305 monotherapy with the ORR and irORR in each cohort of different tumour type **Part II** • To determine CLEVER-1 positivity in each tumour type • To characterize the PK profile of a single dose of FP-1305 after the first dosing for each cohort of different tumour type

	• To characterize the PK profile of FP-1305 during repeated dosing in each cohort of different tumour type • To assess the host immune response to FP-1305 (immunogenicity) in each tumour type • To explore potential predictive markers associated with FP-1305 clinical activity as determined by ORR, CBR and irORR • To investigate the duration of response in the subject group that has a complete or partial response, or stable disease (SD) **Part III** • To characterize population PK of FP-1305 in each selected tumour type during repeated dosing • To assess the host immune response to FP-1305 (immunogenicity) • To assess the duration of response in distinct expansion groups of subjects with advanced solid tumours in CLEVER-1 positive subjects from selected tumour types at a selected dose • To assess progression free survival in subjects who receive at least 1 dose of FP-1305 • To assess the overall survival in subjects who receive at least 1 dose of FP-1305 • To determine the safety and tolerability of FP-1305 during repeated dosing in each tumour type at a selected dose
Endpoints:	<u>Primary outcome measures:</u> **Part I** • Tolerable dose(s) will be determined by the TITE-CRM based on the occurrence/non-occurrence of dose limiting toxicities (DLT) in the trial subjects according to definitions in Section 4.1. **Part II** • Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are collected, graded and reported according to the NCI-CTCAE version 5.0. Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify, record, manage, and analyse the data. Tolerability of new dose(s) will be determined based on the occurrence/non-occurrence of DLT during 28 days following the first dose of FP-1305 in subjects evaluable for DLT assessment in Part II . • The response (ORR, CBR, and irORR separately) to the treatment will be determined by tumour imaging according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 based on images obtained by Cycle 7. Results from each tumour type, dose level and dosing frequency will be reported separately. **Part III** • The response (ORR, CBR and irORR separately) to the treatment will be determined by tumour imaging according to RECIST 1.1 based on images obtained by Cycle 7. Results from each tumour type will be reported separately. <u>Secondary outcome measures:</u> **Part I** • The PK profile of a single dose (during Cycle 1) and repeated doses (during Cycles 1-5) of FP-1305 will be determined by repeated measurements of the drug concentration in the circulation. Peak concentration (Cmax), trough concentration (Cmin), area under the serum concentration versus time curve (AUC), clearance, volume of distribution, and terminal half-life (t1/2) for each dose level will be determined. • Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up.

	• The ORR to the treatment will be determined by tumour imaging according to RECIST 1.1. The CBR is the proportion of subjects that have a complete response, partial response, or stable disease. The irORR will also be calculated. **Part II** • The PK profile of a single dose (during Cycle 1) and repeated doses (during Cycles 2-5) of FP-1305 will be determined by repeated measurements of the drug concentration in the circulation. Peak concentration (Cmax), trough concentration (Cmin), AUC, clearance, volume of distribution, and terminal half-life (t1/2) for each dose level will be determined. Results from each tumour type will be reported separately. • Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up. Results from each tumour type will be reported separately. • Potential genetic, cellular and other predictive markers will be associated with FP-1305 clinical activity as determined by ORR, CBR and irORR. This includes but is not limited to the correlation of response and immune cell profile, cytokine/chemokine profile and the proportion of CLEVER-1-positive monocytes, Cluster of differentiation (CD)4, CD8, their ratio and regulatory T-cells in the circulation and in tumour specimens prior to treatment and in circulation during the first cycle of treatment. • The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout. • Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data. **Part III** • The population PK of FP-1305 will be determined by measurements of the drug concentration in the circulation between Cycles 1 and 5. Results from each tumour type will be reported separately. • Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up. Results from each tumour type will be reported separately. • The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout. • Progression free survival as the time from subject allocation into the trial until documented disease progression according to RECIST 1.1 or death will be measured in the population that has been dosed at least once. • Overall survival is defined as the time from subject allocation into the trial until death from any cause and will be measured in the population that has been dosed at least once. Data will be censored on the last documented data that the subject has been alive. • Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data.
Study population:	Subjects with advanced hepatobiliary tumours (including hepatocellular carcinoma (HCC), gallbladder cancer, intra- and extrahepatic cholangiocarcinoma), pancreatic ductal adenocarcinoma, colorectal adenocarcinoma, serous poorly differentiated (Grade 3) ovarian adenocarcinoma or undifferentiated ovarian cancer, and cutaneous melanoma can participate in Part I of the trial. In addition, subjects with uveal melanoma, gastric adenocarcinoma (including gastro-eosophageal (GE) junction), ER+

	breast cancer and anaplastic thyroid cancer may participate in Parts II and III of the trial.
Phase:	I/II
Description of sites enrolling study subjects:	Approximately 20-30 investigational sites in 5-8 countries located in Europe and in the United States will participate in the trial.
Description of study intervention:	In Part I, the pre-determined dose levels of FP-1305 are 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg and 10.0 mg/kg, and the pre-specified reserve de-escalation or escalation dose levels are 0.05 mg/kg and 0.1 mg/kg or 20 mg/kg, respectively. FP-1305 is administered intravenously every three weeks. In Parts II and III, the dose(s) is based on the results of Part I. Additional doses 30-100 mg/kg are included to be investigated in Part II. However, the maximum amount of FP-1305 in one investigational medicinal product (IMP) infusion is 10 g and cannot be exceeded irrespective of the calculated weight based dose. More frequent dosings (Q1-2W) investigated in Part II are described in Protocol Addendum.
Study duration:	November 2018 – December 2024
Participant duration:	For each subject, the trial will consist of a screening period (maximum 28 days), treatment phase with FP-1305 (one year with potential to continue longer), and a post-treatment period for safety assessment (maximum 4 weeks). Survival data will be collected beyond the subject's active participation in the trial. The collection of the survival data of a subject is limited to 2 years from the first IMP dose or 1 year from the last IMP dose if duration of dosing is more than one year. In case that, as judged by the investigator, it would be beneficial to continue the treatment beyond one year, the protocol allows the treatment according to normal clinical practice, in order to allow the treatment continuation of the study subjects, provided that the clinical development and manufacturing of FP-1305 continues and it is not available via other routes.

1.2 Schema

This is an open label, three-part (Figure 1), Phase I/II, dose-finding and separate cohorts expansion trial to determine the safety, tolerability and preliminary efficacy of repeated doses of CLEVER-1 antibody FP-1305 administered in three-week intervals (Q3W). This interval is called a cycle. In addition to the Q3W dosing , Protocol Addendum introduces once in two weeks (Q2W) and once in week (Q1W) dosing schemes to be investigated. In Part I 30 subjects were enrolled, in Part II up to 10 subjects in each selected Part II cohort (cancer type, dose level and dosing scheme) will be enrolled; in addition, testing of higher doses (30-100 mg/kg) in cohorts with multiple cancer types will proceed in parallel with the treatment of other Part II cohorts. In Part III additional subjects will be enrolled based on the continuation rules set in this protocol. Subjects are enrolled into a specific part of the study and continue in that part until they discontinue (i.e. subjects do not progress from one part to the next). It is estimated that the total number of subjects in the whole trial is up to 700.

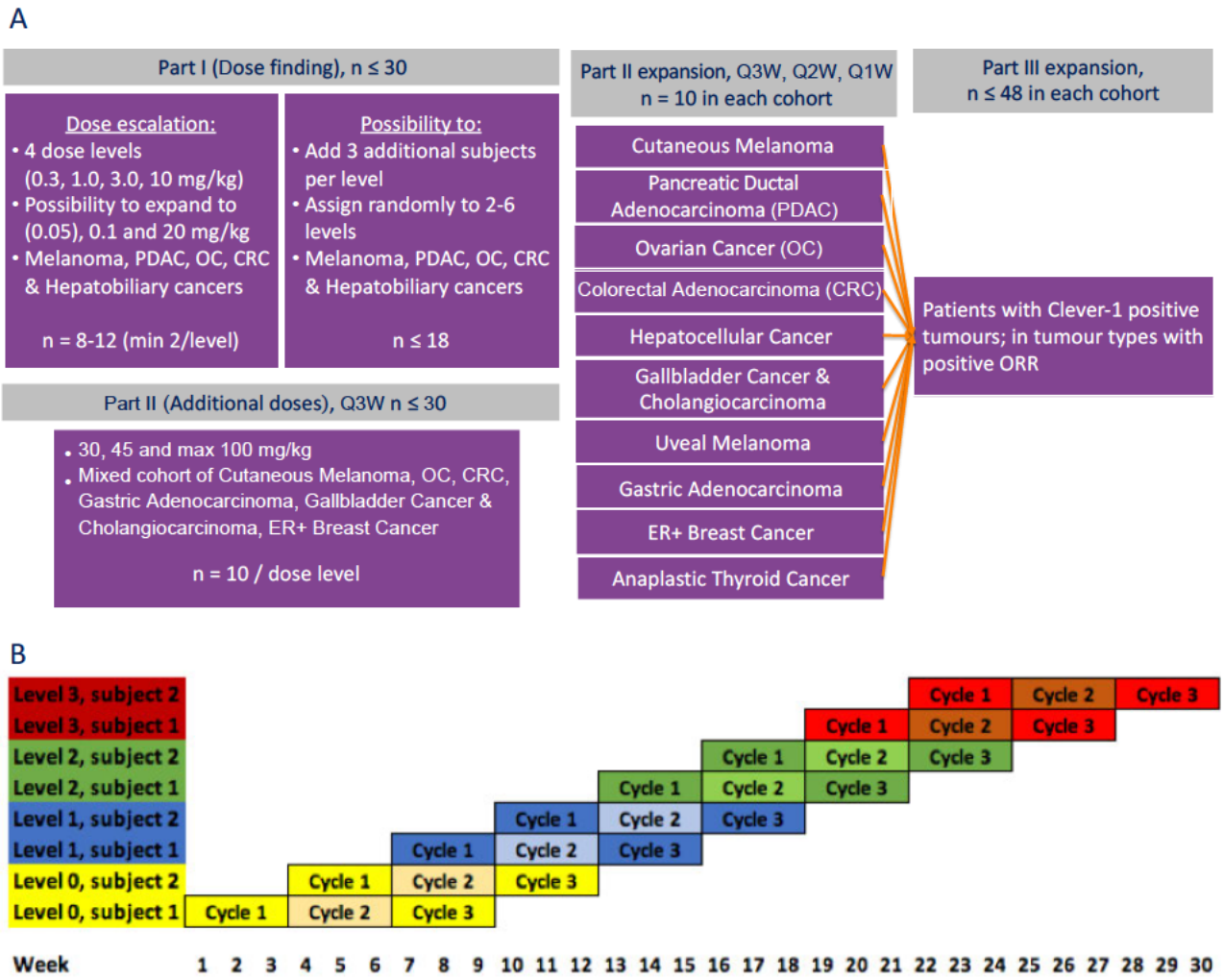

Figure 1: Trial overall schema

A: Overall trial schema. B: Displays the dose-escalation procedure in the absence of DLT in the initial stage in Part I, with a minimum waiting period and DLT assessment period of 3 weeks between subjects. Additional study subjects may be recruited and allocated to MTD or any level below it as deemed necessary to ensure that sufficient amount of scientific data is obtained before selecting the dose for Part II.

1.3 Schedule of Activities

1.3.1 Schedule of Assessment tables for Q3W dosing schema in Parts I-III are shown below (Tables 1-3). Schedule of Assessment tables for Q2W and Q1W schemas in Part II are presented in Protocol Addendum (Tables 1A and 1B).

Table 1: Schedule of Assessments for Part I

Part I Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1, 2 and 4										Cycles 3 and 5-17		Beyond one year in three week cycles	Follow-up[23] ≤ 28 days post treatment
		D1					D2	D3	D4	D5	D8	D15	D1			
		pre[8]	inf	0h	1h	5h							pre	inf		
Informed consent[1]	X															
Inclusion/Exclusion Criteria	X															
IMP administration			X											X	X	
Demographic data	X															
Height		X[C1]														
Vital signs[2,3]	X	X	X	X		X[C1]							X	X	X	X
ECG[4]	X	X		X[C1, C4]									X[C6, C8, C10, C12, C14, C16]			X
Weight	X	X											X		X	
ECOG	X	X											X		X	X
Physical examination	X	X											X		X	X
Medical history	X															
CMV infection status	X															
Urine dipstick test		X											X			
Pregnancy test[5]	X															X

Part I Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1, 2 and 4											Cycles 3 and 5-17		Beyond one year in three week cycles	Follow-up[23] ≤ 28 days post treatment
		D1					D2	D3	D4	D5	D8	D15	D1			
		pre[8]	inf	0h	1h	5h							pre	inf		
PK&ADA																
PK sampling[6]		X		X	X	X	X	X	X	X	X		$X^{C3, C5}$			
ADA sampling[7]		X											$X^{C6, C8, C10, C12, C14, C16}$			X
Blood samples																
HIV serology	X															
Complete Blood Count (CBC)[9]	X	X								X^{C1}			X		X	X
Comprehensive metabolic panel (CMP)[10]	X	X								X^{C1}			X		X	X
Endocrine panel 1[11]	X	$X^{C1,C4}$											X^{C8}			
Endocrine panel 2[12]	X	X											X			
Hepatitis B and C virus[13]	X	X											X^{C6}			
LDH		X											X			X
LDL		X											X			X
AFP (HCC)		X											X			X
CRP		X											X			X
CA-125 (OC)		X											X			X
CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma)		X											X			X
CEA (CRC)		X											X			X

Part I Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1, 2 and 4										Cycles 3 and 5-17		Beyond one year in three week cycles	Follow-up[23] ≤ 28 days post treatment
		D1					D2	D3	D4	D5	D8	D15	D1		
		pre[8]	inf	0h	1h	5h							pre	inf		
Research blood samples																
Receptor occupancy and monocytes (RO assay)[14]		X					$X^{C1,C2}$				$X^{C1, C2}$	$X^{C1, C2}$	X^{C3}			
Oxidized LDL		X											X^{C3}			
Flow cytometry (TBNK- cells and CD127 FOXP3 Assay)[15]		X					$X^{C1,C2}$				$X^{C1, C2}$	$X^{C1, C2}$	X^{C3}			
Cytokine and chemokine panel[16]		X									$X^{C1, C2}$	$X^{C1, C2}$	X^{C3}			
Blood sample for PBMC isolation[17]		$X^{C1, C4}$								X^{C1}						
PD markers -Tissue																
Tumour biopsy[18]	X						X^{C2}									
Imaging																
Tumour imaging [19, 20]		$X^{C1, C4}$											$X^{C7, C10, C13, C16}$		X	
Brain imaging[21]	X															
AE assessment[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X											X			X

D=Day, h=Hour, Pre=pre IMP infusion, inf=IMP infusion start, 0h=immediately after the IMP infusion completion and infusion line flushing, 1h=1h after the IMP infusion completion, 5h=5h after the infusion completion, X^{Cn} Done only in particular cycle (n)

See the Laboratory Manual for sample collection and handling procedures in detail.

[1] Main ICF must be signed by the subject before any trial related procedures can be initiated. Genetic ICF is voluntary.

[2] Vital signs: blood pressure, heart rate, temperature, respiratory rate

[3] Cycles 1-3 vital signs to be taken before IMP administration, and during IMP infusion every 20 minutes for 1 h (3 additional readings, the third additional measurement should be performed after the IMP infusion has completed; therefore if the infusion lasts more than 1 h, then the third additional measurement may be more than 20 minutes after the

second additional measurement), and in Cycle 1 at 5 h (+/- 2 h) after IMP infusion completion. After Cycle 3 vital signs to be taken before and after IMP administration only and if clinically indicated

[4] Predose assessment at screening, Cycles 1, 2, 4, 6, and every second cycle thereafter; and Follow-up; postdose assessment at Cycles 1 and 4; ECG must be performed also always if clinically indicated

[5] Pregnancy test (serum) for women of child-bearing potential only

[6] Cycles 1, 2, 3, 4 and 5 only; Post IMP administration timepoints in Cycles 1, 2 and 4: 0 h after infusion and flushing the line, 1 h (+/- 5 mins), 5 h (+/- 30 mins), D2 (+/- 4 h), D3 (+/- 4 h), D4 (+/- 4 h), D5 (+/- 8 h), and D8 (+/- 24 h)

[7] Cycles 1, 2, 4, 6, and every second cycle thereafter, or if clinically indicated, and Follow-up

[8] Predose assessments, local and research laboratory blood samples are permitted to be taken up to three days before the Day 1 of each cycle. The only exception is vital signs which should be taken on the day of IMP administration

[9] Complete blood cell counts: white blood cells, neutrophils, lymphocytes, platelets, haemoglobin

[10] Comprehensive metabolic panel: glucose, calcium, sodium, potassium, chloride, creatinine, ALT, ALP, AST, CK, total bilirubin, albumin

[11] Endocrine panel 1: Cortisol, lipase and amylase (pancreas specific) on cycles 1, 4 and 8 and when clinically indicated

[12] Endocrine panel 2: thyroid stimulating hormone, PTH, free thyroxine (T4), free triiodothyronine (T3) on each cycle

[13] Screening test may be immunochemical. If positive, nucleic acid test should be performed on Cycles 1, 2, 4 and 6. If negative at screening no additional tests should be performed

[14] Predose assessment in Cycles 1, 2, 3 and 4. Post IMP administration timepoints in Cycles 1 and 2: D2 (+/- 4 h), D8 (+/- 24 h), and D15 (+/- 24 h)

[15] Predose assessment in Cycles 1, 2, 3 and 4. Post IMP administration timepoints in Cycles 1 and 2 D2 (+/- 4 h), D8 (+/- 24h) and D15 (+/- 24 h)

[16] Predose assessment in Cycles 1, 2, 3 and 4. Post IMP administration timepoints in Cycles 1 and 2 D8 (+/-24 h) and D15 (+/- 24 h)

[17] Predose assessment in Cycles 1 and 4. Post IMP administration timepoints in Cycle 1 D5 (+/- 4 h)

[18] First tumour biopsy must be less than 6 months old from the date of consent or taken during the screening period. In addition, an archival block may be used if needed; the biopsy in Cycle 2 within 10 days after the IMP administration.

[19] The same imaging method (CT, MRI) per subject must be used throughout the trial. First scan (C1) must be less than 6 weeks prior the first dose (routine diagnostic image can be used); the scans in other cycles within +/- 10 days from the IMP administration

[20] Cycles 4, 7, 10, and every third cycle thereafter, up to one year. If the treatment extends beyond one year, 18- (± 1 month) and 24- (± 1 month) month images are mandatory to take if not routinely taken at these timepoints. In addition to the imaging time-points specified here, also any other imaging performed by the site will also be collected.

[21] Brain imaging (CT) for exclusion of CNS metastasis. Routine diagnostic image (CT/MRI) can be used if available within two weeks prior to the date of consent or done during the screening period.

[22] All subjects in the dose-escalation cohorts should be closely monitored for safety for the first 24 h after the first IMP infusion and for a minimum of 6 h after the second IMP infusion at the trial site hospital. Subjects in the dose-expansion cohorts should be monitored for a minimum of 6 h after the first and the second IMP infusions at the trial site hospital. After Cycle 2 all subjects should be observed for a minimum of 2 h after the IMP infusions. Post-dose observation will be longer if deemed appropriate. AE assessment done if visit indicated.

[23] Follow-up visit will be performed for 3 weeks (+/- 1 week) after the decision to discontinue the IMP. In addition, survival data will be collected for up to 2 years post the first IMP dose (at 1 year and 2 years after the first IMP dose), or 1 year from the last IMP dose if duration of dosing is more than one year.

Table 2: Schedule of Assessments for Part II

Part II Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1 and 2											Cycles 3-17		Beyond one year in three week cycles	Follow-up[23] (4 weeks [± 1 week] after last dose)
		D1					D2	D3	D4	D5	D8	D15	D1			
		pre[8]	inf	0h	1h	5h							pre	inf		
Informed consent[1]	X															
Inclusion/Exclusion Criteria	X															
IMP administration			X											X	X	
Demographic data	X															
Height		X[C1]														
Vital signs[2,3]	X	X	X	X		X[C1]							X	X	X	X
ECG[4]	X	X		X[C1]									X[C4, C6, C8, C10, C12, C14, C16]	X[C4]		X
Weight	X	X											X		X	
ECOG	X	X											X		X	X
Physical examination	X	X											X		X	X
Medical history	X															
CMV infection status	X															
Urine dipstick test		X											X			
Pregnancy test[5]	X	X											X		X	X
PK&ADA																
PK sampling[6]		X		X	X	X	X	X	X	X	X		X[C3, C4]			
ADA sampling[7]		X											X[C4, C6, C8, C10, C12, C14, C16]			X

Part II Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1 and 2										Cycles 3-17		Beyond one year in three week cycles	Follow-up[23] (4 weeks [± 1 week] after last dose)
		D1					D2	D3	D4	D5	D8	D15	D1			
		pre[8]	inf	0h	1h	5h							pre	inf		
Blood samples																
HIV serology	X															
Complete Blood Count (CBC)[9]	X	X								X[C1]			X		X	X
Comprehensive metabolic panel (CMP)[10, 11]	X	X								X[C1]	X[C2]		X[11]		X	X
Endocrine panel[12]	X	X											X			
Hepatitis B and C virus [13]	X	X											X[C4, C6]			
LDH		X											X			X
LDL Cholesterol		X											X			X
AFP (HCC)		X											X			X
CRP		X											X			X
CA-125 (OC)		X											X			X
CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adeno-carcinoma)		X											X			X
CEA (CRC, ER+ BC, gastric adenocarcinoma)		X											X			X
CA-15-3 (ER+ BC)		X											X			X

Part II Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1 and 2										Cycles 3-17		Beyond one year in three week cycles	Follow-up[23] (4 weeks [± 1 week] after last dose)
		D1					D2	D3	D4	D5	D8	D15	D1		
		pre[8]	inf	0h	1h	5h							pre	inf		
Research blood samples																
Blood sample for RO and PBMC[14]		X					X^{C1}				X^{C1}	X^{C1}				
Blood sample for PBMC isolation [15]		X					X^{C1}				X^{C1}	X^{C1}				
sCLEVER-1 RO[16]		X					X				X	X	X^{C3}			
Oxidized LDL		X											$X^{C3, C4}$			
Flow cytometry (TBNK- cells, CD127 FOXP3 Assay and PD-1 T-Helper Assay)[17]		X					X				X	X	$X^{C3, C4}$			
Cytokine and chemokine panel[18]		X									X	X	$X^{C3, C4}$			
ctDNA (requires genetic consent)		X											X^{C3}			
PD markers -Tissue																
Tumour biopsy[19]	X			X^{C2}												
Imaging																
Tumour imagin[20, 21]		X^{C1}											$X^{C4, C7, C10, C13, C16}$		X	
Brain imaging[22]	X															
AE assessment[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X											X			X

D=day, H=hour, Pre=pre IMP infusion, inf=IMP infusion start, 0h=immediately after all IMP has been administered, 1h=1h after the IMP infusion, 5h=5h after the infusion, X^{Cn} Done only in particular cycle (n)

See the Laboratory Manual for sample collection and handling procedures in detail.

[1] Main ICF must be signed by the subject before any trial related procedures can be initiated. Genetic ICF is voluntary.

[2] Vital signs: blood pressure, heart rate, temperature, respiratory rate

[3] Cycles 1-3 vital signs to be taken at the following 4 time-points: prior to the start of the infusion, 20 minutes after the start of the infusion, 40 minutes after the start of the infusion and at 1 h after the start of the infusion or at the end of the infusion (immediately after flushing the line), whichever occurs later, and in Cycle 1 at 5 h (+/- 2 h) after IMP infusion completion. After Cycle 3 vital signs to be taken before and after IMP administration only and at additional time-points if clinically indicated

[4] Predose assessment at screening, Cycles 1, 2, 4, 6, and every second cycle thereafter; and Follow-up; postdose assessment at Cycles 1 and 4; ECG must be performed also always if clinically indicated

[5] Pregnancy test for women of child-bearing potential only. Screening and Follow-up visit: test in serum, Predose assessments: test in serum or urine.

[6] Cycles 1, 2, 3 and 4 only; Post IMP administration timepoints in Cycles 1 and 2: 0 h after infusion and flushing the line, 1 h (+/- 5 mins), 5 h (+/- 30 mins), D2 (+/- 4 h), D3 (+/- 4 h), D4 (+/- 4 h), D5 (+/- 8 h), and D8 (+/- 24 h)

[7] Cycles 1, 2, 4, 6, and every second cycle thereafter, or if clinically indicated, and Follow-up

[8] Predose assessments, local and research laboratory blood samples are permitted to be taken up to three days before the Day 1 of each cycle. The only exception is vital signs which should be taken on the day of IMP administration

[9] Complete blood cell counts: white blood cells, neutrophils, lymphocytes, platelets, haemoglobin

[10] Comprehensive metabolic panel: glucose, calcium, sodium, potassium, chloride, creatinine, ALT, ALP, AST, CK, total bilirubin, albumin.

[11] Screening, predose at every cycle; postdose at Cycle 1 D5 (+/- 8 h), Cycles 2 and 3 D8 (+/- 24 h), and Follow-up

[12] Endocrine panel: cortisol, lipase and pancreas-specific amylase, thyroid stimulating hormone, PTH, free thyroxine (T4), free triiodothyronine (T3), troponin on all cycles

[13] Screening test may be immunochemical. If positive, nucleic acid test should be performed on Cycles 1, 2, 4 and 6. If negative at screening no additional tests should be performed

[14] At selected sites and cohorts only. Predose assessment in Cycles 1 and 2. Post IMP administration timepoints in Cycle 1: D2 (+/- 4 h), D8 (+/- 24 h), and D15 (+/- 24 h)

[15] Collected at sites that do not collect 'Blood sample for RO and PBMC' (see footnote 14 above). Predose assessment in Cycles 1 and 2. Post IMP administration timepoints in Cycle 1: D2 (+/- 4 h), D8 (+/- 24 h), and D15 (+/- 24 h)

[16]Analysed from the plasma fraction of the blood sample collected for PBMC isolation or blood sample for RO and PBMC during Cycle 1 predose, D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h) and Cycle 2 predose. Collected as an independent sample in Cycle 2 D2 (+/- 4 h), D8 (+/- 24 h), D15 (+/- 24 h), and Cycle 3 predose. See Central Laboratory Services manual for further details.

[17] Predose assessment in Cycles 1, 2, 3 and 4. Post IMP administration timepoints in Cycles 1 and 2 D2 (+/- 4 h), D8 (+/- 24h) and D15 (+/- 24 h)

[18] Predose assessment in Cycles 1, 2, 3 and 4. Post IMP administration timepoints in Cycles 1 and 2 D8 (+/-24 h) and D15 (+/- 24 h)

[19] First tumour biopsy must be less than 6 months old from the date of consent or taken during the screening period. In addition, an archival block may be used if needed; the biopsy in Cycle 2 within 10 days after the IMP administration. Biopsy from new lesions is recommended if assessed feasible by the investigator considering the location of the lesions and condition of the subject.

[20]The same imaging method (CT, MRI) per subject must be used throughout the trial. First scan (C1) must be less than 6 weeks prior the first dose (routine diagnostic image can be used); the scans in other cycles within +/- 10 days from the IMP administration

[21] Cycles 1, 4, 7, 10, and every third cycle thereafter, up to one year. If the treatment extends beyond one year, 18- (± 1 month) and 24- (± 1 month) month images are mandatory to take if not routinely taken at these timepoints. In addition to the imaging time-points specified here, also any other imaging performed by the site will also be collected.

[22]Brain imaging (CT) for exclusion of CNS metastasis. Routine diagnostic image (CT/MRI) can be used if available. The brain scan within six weeks prior to the 1st dose is acceptable.

[23] First three subjects testing new doses or dosing frequencies in Part II should be closely monitored for safety for the first 24 h after the first IMP infusion and for a minimum of 6 h after the second IMP infusion at the trial site hospital. Other subjects in Part II will be monitored for a minimum of 6 h after the first IMP infusion. After Cycle 1 all subjects should be observed for a minimum of 2 h after the IMP infusions. In any part of the trial, post-dose observation will be longer if deemed appropriate. AE assessment done if visit indicated.

[24] Once it has been decided that a patient will permanently stop treatment, a Follow-up Visit should be performed 4 weeks (+/- 1 week) after their last dose of IMP. If the last IMP dose was >5 weeks at the time of the decision, the Follow-up Visit should be performed as soon as possible In addition, survival data will be collected for up to 2 years post the first IMP dose (at 1 year and 2 years after the first IMP dose), or 1 year from the last IMP dose if duration of dosing is more than one year.

Table 3: Schedule of Assessments for Part III

Part III Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1, 2 and 4								Cycles 3 and 5-17		Beyond one year in three week cycles	Follow-up (4 weeks [± 1 week] after last dose)[25]
		D1			D2	D3	D5	D8	D15	D1			
		pre[11]	inf	4h						pre	inf		
Informed consent[1]	X												
Inclusion/Exclusion Criteria	X												
IMP administration			X								X	X	
Demographic data	X												
Height		X^{C1}											
Vital signs[2, 3]	X	X	X							X	X	X	X
ECG[4]	X									X^{C5}			
Weight	X	X								X		X	
ECOG	X	X								X		X	X
Physical examination	X	X								X		X	X
Medical history	X												
CMV infection status	X												
Pregnancy test[5]	X	X								X		X	X
PK&ADA													
PK sampling (group A)[6,7]		X^{C1}		X^{C2}	X^{C1}	X^{C4}	X^{C1}						
PK sampling (group B)[8, 9]		X^{C4}		X^{C1}	X^{C2}	X^{C1}	X^{C4}						
ADA sampling[10]		$X^{C1, C2}$								$X^{C5,C8, C11, C14, C17}$			X
Blood samples													
HIV serology	X												
Complete Blood Count (CBC)[12]	X	X								X		X	X

Part III Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1, 2 and 4								Cycles 3 and 5-17		Beyond one year in three week cycles	Follow-up (4 weeks [± 1 week] after last dose)[25]
		D1			D2	D3	D5	D8	D15	D1			
		pre[11]	inf	4h						pre	inf		
Comprehensive metabolic panel (CMP)[13, 14]	X	X					X^{C1}	X^{C2}		X^{14}		X	X
Endocrine panel[15]	X	X								X			
Hepatitis B and C virus [16]	X	X								X^{C6}			
LDH		X								X			X
LDL Cholesterol		X								X			X
AFP (HCC patients)		X								X			X
CRP		X								X			X
CA-125 (OC patients)		X								X			X
CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma)		X								X			X
CEA (CRC, ER+ BC, gastric adenocarcinoma)		X								X			X
CA-15-3 (ER+ BC)		X								X			X
Research blood samples													
Blood sample for PBMC isolation[17]		$X^{C1, C4}$						X^{C1}					
Oxidized LDL		X								X^{C3}			
Flow cytometry (TBNK- cells, CD127 FOXP3 Assay and PD-1 T-Helper Assay)[18]		$X^{C1, C2}$						X^{C1}	X^{C1}				

Part III Q3W	Screening ≤ 28 days prior to Day 1	Cycles 1, 2 and 4								Cycles 3 and 5-17		Beyond one year in three week cycles	Follow-up (4 weeks [± 1 week] after last dose)[25]
		D1			D2	D3	D5	D8	D15	D1			
		pre[11]	inf	4h						pre	inf		
Cytokine and chemokine panel[19]		$X^{C1, C2}$						X^{C1}	X^{C1}				
ctDNA (requires genetic consent)		$X^{C1, C2}$								X^{C3}			
PD markers -Tissue													
Tumour biopsy[20]	X		X^{C2}										
Imaging													
Tumour imaging [21, 22]		$X^{C1, C4}$								$X^{C7, C10, C13, C16}$		X	
Brain imaging [23]	X												
AE assessment[24]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X								X			X
D=day, H=hour, Pre=pre IMP infusion, inf=IMP infusion start, 4h=4h after the IMP infusion, X^{Cn} Done only in particular cycle (n)													

See the Laboratory Manual for sample collection and handling procedures in detail.

[1] Main ICF must be signed by the subject before any trial related procedures can be initiated. Genetic ICF is voluntary.

[2] Vital signs: blood pressure, heart rate, temperature, respiratory rate

[3] Cycles 1-3 vital signs to be taken at the following 4 time-points: prior to the start of the infusion, 20 minutes after the start of the infusion, 40 minutes after the start of the infusion and at 1 h after the start of the infusion or at the end of the infusion (immediately after flushing the line), whichever occurs later, and in Cycle 1 at 5 h (+/- 2 h) after IMP infusion completion. After Cycle 3 vital signs to be taken before and after IMP administration only and at additional time-points if clinically indicated

[4] Screening and Cycle 5; in addition, ECG must be performed also always if clinically indicated

[5] Pregnancy test for women of child-bearing potential only. Screening and Follow-up visit: test in serum, Predose assessments: test in serum or urine.

[6] PK (group A): subjects with odd trial numbers: C1Pre, C1D2, C1D5, C2D1(4h), C4D3.

[7] At timepoints C1D2 and C2D1 4h +/- 2 h is allowed (i.e. 2–6 h after IMP administration). At timepoints C1D5 and C4D3 +/- 24 h are allowed (i.e. +/- 1 days)

[8] PK (group B): subjects with even trial numbers: C1D1(4h), C1D3, C2D2, C4Pre, C4D5

[9] At timepoints C1D1(4h) and C2D2 +/- 2 h is allowed (i.e. 2–6 h after IMP administration)At timepoints C1D3, C4D5 +/- 24 h are allowed (i.e. +/- 1 days)

[10] Cycles 1, 2, 5, 8, and every third cycle thereafter, or if clinically indicated, and Follow-up

[11] Predose assessments and local laboratory and research blood samples are permitted to be taken up to three days before the Day 1 of each cycle

[12] Complete blood cell counts: white blood cells, neutrophils, lymphocytes, thrombocytes, haemoglobin

[13] Comprehensive metabolic panel: glucose, calcium, sodium, potassium, chloride, creatinine, ALT, ALP, AST, CK, total bilirubin, albumin
[14] Screening, predose at every cycle; postdose at Cycle 1 D5 (+/- 8 h), Cycles 2 and 3 D8 (+/- 24 h), and Follow-up
[15] Endocrine panel: cortisol, lipase and pancreas-specific amylase, thyroid stimulating hormone, PTH, free thyroxine (T4), free triiodothyronine (T3), troponin on all cycles
[16] Screening test may be immunochemical. If positive, nucleic acid test should be performed on Cycles 1, 2, 4 and 6. If negative at screening no additional tests should be performed
[17] Predose assessment in Cycles 1 and 4. Post IMP timepoint in Cycle 1 D8 (+/- 24 h).
[18] Predose assessment in Cycles 1 and 2. Post IMP administration timepoints in Cycle 1 D8 (+/- 24h) and D15 (+/- 24 h)
[19] Predose assessment in Cycles 1 and 2. Post IMP administration timepoints in Cycle 1 D8 (+/-24 h) and D15 (+/- 24 h)
[20] First tumour biopsy must be less than 6 months old from the date of consent or taken during the screening period. In addition, an archival block may be used if needed; the biopsy in Cycle 2 within 10 days after the IMP administration. Biopsy from new lesions is recommended if assessed feasible by the investigator considering the location of the lesions and condition of the subject.
[21] The same imaging method (CT, MRI) per subject must be used throughout the trial. First scan (C1) must be less than 6 weeks prior the first dose (routine diagnostic image can be used); the scans in other cycles within +/- 10 days from the IMP administration
[22] Cycles 1, 4, 7, 10, and every third cycle thereafter, up to one year. If the treatment extends beyond one year, 18- (± 1 month) and 24- (± 1 month) month images are mandatory to take if not routinely taken at these timepoints
[23] Brain imaging (CT) for exclusion of CNS metastasis. Routine diagnostic image (CT/MRI) can be used if available. The brain scan within six weeks prior to the 1st dose is acceptable
[24] All subjects will be monitored for minimum of 4 h after the first IMP infusion. After Cycle 1 subjects should be observed for a minimum of 2 h after the IMP infusions. Post-dose observation will be longer if deemed appropriate. AE assessment done if visit indicated.
[25] Once it has been decided that a patient will permanently stop treatment, a Follow-up Visit should be performed 4 weeks (+/- 1 week) after their last dose of IMP. If the last IMP dose was >5 weeks at the time of the decision, the Follow-up Visit should be performed as soon as possible. In addition, survival data will be collected for up to 2 years post the first IMP dose (at 1 year and 2 years after the first IMP dose), or 1 year from the last IMP dose if duration of dosing is more than one year.

2 BACKGROUND AND RATIONALE

2.1 Immunotherapy for Cancer

In recent years, there have been major breakthroughs in harnessing the immune system to treat cancer. Cancer research prior to this has successfully identified many of the pathways which drive malignant cell transformation and we now know the genetic aberrations which drive most cancers. Unfortunately, therapies for many cancers still remain ineffective or only demonstrate short term effectiveness. It is now increasingly understood that the tumour microenvironment (TME) is a vital player in the growth, progression and response to treatment of most cancers (Balkwill et al. 2012). It is clear that the TME helps malignant cells avoid immune destruction. The TME broadly comprises angiogenic cells, stromal cells and infiltrating immune cells (Hanahan et al. 2012). Neovascularization of the tumour has long been known to be crucial for cancer progression (Folkman et al. 1989) and more recently it is clear that tumour endothelial cells can actively secrete growth promoting factors (Butler et al. 2010). There is also evidence that stromal cells around tumours have a particular phenotype which also release pro-tumorigenic factors such as promoters of growth, migration and epithelial-mesenchymal transformation and are termed cancer-associated fibroblasts (Hanahan et al. 2011). These factors lead to an immune environment that reflects wound healing and is characterised by populations of immune cells that suppress excessive immune activation including regulatory T cells, myeloid derived suppressor cells, alternatively activated macrophages and immature dendritic cells which prevent cytotoxic T cells and Natural Killer /T cells from eradicating tumour cells (Ruffell et al. 2010). Several molecular receptors on immune cells play a role in balancing the effector (tumour killing) and suppressive (tumour-promoting) actions of T cells. Two examples on lymphocytes are the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor and the programmed cell death receptor-1 (PD-1) (Pardoll 2012). They have been termed immune checkpoints and monoclonal antibodies have been developed to block their actions, this has led to several successful clinical studies in cancers, and European Medicines Agency/U.S. Food and Drug Administration approval for their use in malignant melanoma, lung cancer, and other malignancies (Garon et al. 2015; Hodi et al. 2010; Robert et al. 2015).

There is also gathering evidence that other immune cells such as macrophages also play a critical role in promoting the growth and spread of cancers to distant sites (Qian et al. 2010). Nonclinical studies have now confirmed that macrophages in the TME, termed tumour associated macrophages (TAMs) have several properties which allow tumour escape from immune destruction (Curiel et al. 2004; DeNardo et al. 2011).

Cancer immunotherapy, particularly checkpoint inhibition, has evolved to a key part of the clinical management of cancer. PD-1 blockade is generally well tolerated and may induce durable tumour control. However, the majority of cancers does not respond to current immunotherapy or eventually develop treatment resistance.

Macrophages are key cells in the control of the immune system activation. They play a dual role in the host defence. They form the first line of defence as a component of the innate immune response and act as important accessory cells in the adaptive immune response. During immune system activation, cells of the monocyte lineage define the direction and the magnitude of the immune reaction. Pro-inflammatory macrophages (M1) cells amplify the immune activation during inflammation, whereas alternatively activated immunosuppressive macrophages (M2) contribute during the healing phase. Most of the tumour associated macrophages that infiltrate the tumour have the M2 phenotype and promote tumour progression (Mantovani et al. 2002).

Tumours that are resistant to PD-1-related therapy often induce the downregulation of the expression of important molecules in the antigen presentation pathway, including the major histocompatibility complex class I and II, as well as β2-microglobulin, most likely due to the reduced production of interferon (IFN)-γ (Wang et al. 2016). Therapies that increase IFN-γ production and/or eliminate M2 macrophages to boost the function of immune system may be used either alone or in combination with PD-1 blockage to achieve cancer elimination. The elimination of M2 macrophages by different colony stimulating factor 1 receptors (CSF1R) targeting antibodies and small molecular inhibitors are currently investigated in several clinical trials. However, the elimination of highly immunosuppressive tumour associated macrophages appears to be extremely difficult with this strategy (Pradel et al. 2016). Thus, alternative strategies to target tumour associated M2 macrophages are needed.

2.2 CLEVER-1 and FP-1305

2.2.1 Background to CLEVER-1

CLEVER-1, also known as Stabilin-1, STAB1, FEEL-1, or KIAA0246, is a 280 kilodalton multifunctional type-1 transmembrane protein with a large extracellular part containing clusters of epidermal growth factor-like domains, seven fasciclin domains, and one X-link domain. CLEVER-1 deficient mice do not display any obvious physical or behavioural abnormalities and breed comparably to wild type control animals on C57BL/6 as well as Balb/c genomic background (Schledzewski et al. 2011). CLEVER-1 deficient mice demonstrate mildly increased fibrogenesis within the liver parenchyma, which is otherwise normal (Schledzewski et al. 2011; Rantakari et al. 2016).

CLEVER-1 is expressed in the following human structures or cells: specialised vascular beds of the liver, lymph, adrenal cortex and spleen (sinusoidal endothelium), and sub-populations of tissue resident macrophages. Stabilin-2 is highly expressed in non-continuous sinusoidal endothelium of liver, lymph node, spleen and bone marrow.

In human monocyte-derived macrophages, CLEVER-1 protein can be detected after the cells have been stimulated with interleukin (IL)-4 in combination with dexamethasone or with dexamethasone alone, whereas IFN-γ has a negative effect on CLEVER-1 expression. CLEVER-1 is expressed on M2 tissue macrophages and sinusoidal endothelial cells in the human spleen, liver, adrenal cortex, lymph nodes, and bone marrow as well as on the lymphatic endothelium. In kinetic analyses of tumours on days 3, 6, and 10, the first macrophage mannose receptor (MRC)-positive M2 macrophages were seen in day 6 samples, whereas CLEVER-1 was first detected on macrophages in day 10 samples. CLEVER-1–positive monocytes can also be detected in the circulation of tumour-bearing mice. All tumour associated CLEVER-1-positive macrophages are MRC-positive, but only about 50% of these macrophages express CLEVER-1. Low pH induces CLEVER-1 expression (Park et al. 2012). Thus, CLEVER-1 is also expressed on blood vessels in various angiogenic conditions, including during wound healing, tumour vascularization, and chronic inflammation of the skin, such as psoriasis.

CLEVER-1 supports transendothelial migration of CD4 FoxP3+ regulatory T cells across hepatic sinusoidal endothelial cells (Shetty et al. 2011). It is also highly expressed in a subset of tumour associated macrophages (David et al. 2012). High expression of CLEVER-1 on the surface of macrophages suppresses the activation of Th1 lymphocytes. Blocking of CLEVER-1 on macrophages leads to increased IFN-γ and decreased IL-4 production in a T-cell co-culture (Palani et al. 2016).

In different tumour models, CLEVER-1 controls cancer growth and metastasis. In these models, the density of F4/80 and MRC-positive macrophages and FoxP3-positive T cells in the primary tumours as well as in metastases is diminished in the absence of CLEVER-1. Importantly, the numbers of intratumoural CD3- and CD8-expressing T cells are not affected, indicating that the immune balance is changed (Karikoski et al. 2014).

In sum, these findings lend support to a hypothesis that blocking of CLEVER-1 with an anti-CLEVER-1 antibody, such as FP-1305, will lead to immune system activation, which, in turn, may lead to cancer elimination.

2.2.2 CLEVER-1 Antibody FP-1305

The IMP, FP-1305 is a humanized IgG4 antibody that binds to a discontinuous epitope in the FAS1/FAS2 domains of human CLEVER-1. The IMP is manufactured by Patheon (Patheon S.p.A. Italia, part of Thermo Fisher Scientific), II Trav. SX Via Morolense 5, 03013 Ferentino FR, Italy. The IMP is a sterile clear to opalescent solution. Each 10 mL glass vial contains 250 mg of FP-1305 in histidine buffer containing stability increasing excipients. The concentration of FP-1305 in the formulation is 25 mg/mL. Further details are available in Investigator's Brochure of FP-1305.

The IMP will be administered intravenously over approximately 40-120 minutes infusion according to the dosing schedule (Q3W, Q2W or Q1W).

The IMP will be delivered to the hospital pharmacy. In clinical trials, FP-1305 is stored at 2-8 °C. After preparing the infusion, the IMP must be administered during the same day. The shelf-life and detailed instructions for the handling of the IMP are given in the Pharmacy Manual.

2.2.3 Nonclinical Data of CLEVER-1 Inhibition and FP-1305

The role of CLEVER-1 has been evaluated in mice. Gene knockout studies have demonstrated that mice deficient of CLEVER-1 are phenotypically normal except for healing from experimental liver injury. Since CLEVER-1 deficient mice do not display any clear phenotype when grown in normal conditions, it is believed that CLEVER-1 blockage with FP-1305 will be safe. Redundant functions of CLEVER-1 and Stabilin-2 and their similar expression in the sinusoidal endothelium may well explain that no clear phenotype is observed in CLEVER-1 deficient mice (Schledzewski et al. 2011). CLEVER-1 deficiency, or inhibition of CLEVER-1 in mouse tumour models, leads to decreased tumour growth and metastasis potential, but does not affect bacterial clearance or immunisation of the animals (Karikoski et al. 2009; Karikoski et al. 2014). In addition, CLEVER-1 inhibition did not modify the disease course (neither severity nor incidence) of neutrophil- or lymphocyte-dominated models of arthritis, induced by anti-collagen II antibodies (leading to collagen antibody-induced arthritis) or collagen type I (leading to collage-induced arthritis), respectively. Similar results were also obtained in arthritis experiments performed with Ncf1-mutated mice, which normally display a severe form of collage-induced arthritis (Karikoski et al. 2014).

In vitro, an α-CLEVER-1 antibody blocks the transendothelial migration of CD4 lymphocytes through hepatic sinusoidal endothelial cells, whereas CD8 T cell migration remains unchanged. Especially the migration of CD4+CD25+FoxP3+ Tregs is significantly blocked, whereas the migration of CD4+CD25+-cells is not (Shetty et al. 2011). The same antibody also blocks the adhesion of tumour cells to the lymphatic endothelium of lymph nodes or on the endothelium of the high endothelial venule-like vessels (Irjala, Alanen, et al. 2003).

Peripheral blood mononuclear cells (PBMCs) blocked with an anti-CLEVER-1 antibody *in vitro* at the concentration of 20 μg/mL produced high numbers of IFN-γ spot forming cells in comparison to PBMCs treated with control antibodies in tetanus toxoid re-stimulation experiments. It was concluded that the ligation of CLEVER-1 on monocytes with a function blocking antibody shifts the antigen specific recall response to a pro-inflammatory Th1 direction (Palani et al. 2016).

In vivo, the FP-1305 antibody binds CLEVER-1 on lymphatic sinuses, and controls lymphocyte trafficking in lymph nodes (Irjala, Elima, et al. 2003). In addition, the antibody blocked the trafficking of EL-4 lymphoma cells from the footpad to the draining popliteal lymph nodes (Karikoski et al. 2014).

2.3 Rationale for Targeting CLEVER-1 in the Tumour Microenvironment

CLEVER-1 is expressed on sinusoidal endothelium and subsets of macrophages (Kzhyshkowska 2010). On the endothelium, it functions as an adhesion receptor and mediates the transmigration of lymphocytes, and on macrophages it functions as a scavenger receptor for several ligands including acetylated low density lipoproteins (LDLs), SPARC and placental lactogen (Kzhyshkowska 2010; Salmi et al. 2004). Several features of CLEVER-1 function demonstrate that it has pro-tumourigenic and pro-metastatic properties: 1) On the liver endothelium it has been shown to specifically support the recruitment of regulatory T cells (Shetty et al. 2011), 2) It has been shown to directly mediate the binding of cancer cells to lymphatic endothelium (Irjala, Alanen et al. 2003), 3) It is expressed on type 2 macrophages and found at sites of several human cancers as well as on tumour associated vessels (Palani et al. 2011; Algars et al. 2012; Ammar et al. 2011).

Subsequent functional interventions which inhibited CLEVER-1 in nonclinical studies confirmed that blocking CLEVER-1 is a potential therapeutic strategy for treating cancers and metastatic spread. These included studies with human monocytes which confirmed that CLEVER-1 on macrophages suppress Th1 activation of lymphocytes and could be reversed with antibody blockade (Palani et al. 2016). In vivo animal models of malignant melanoma and lymphoma were used to demonstrate that CLEVER-1 antibody blockade could successfully inhibit tumour progression (Karikoski et al. 2014). These studies support the role of CLEVER-1 as a tissue microenvironmental promoter of cancer and its blockade as a novel anti-cancer therapy. Our data from human tumours also supports the hypothesis that CLEVER-1 promotes an immunosuppressive environment around tumours. Using tissue samples from patients with a primary liver cancer, it was shown that CLEVER-1 is expressed on tumour associated vessels and macrophages. It was further identified, that tumours with high CLEVER-1 expression in the peri-tumoral region correlated with a high regulatory T cell/ CD8 cytotoxic T cell ratio, which favours an immunosuppressive environment. Tumours with high CLEVER-1 expression in the peri-tumoral region also had poor prognostic markers, such as poor differentiation and microvascular invasion (Figure 2).

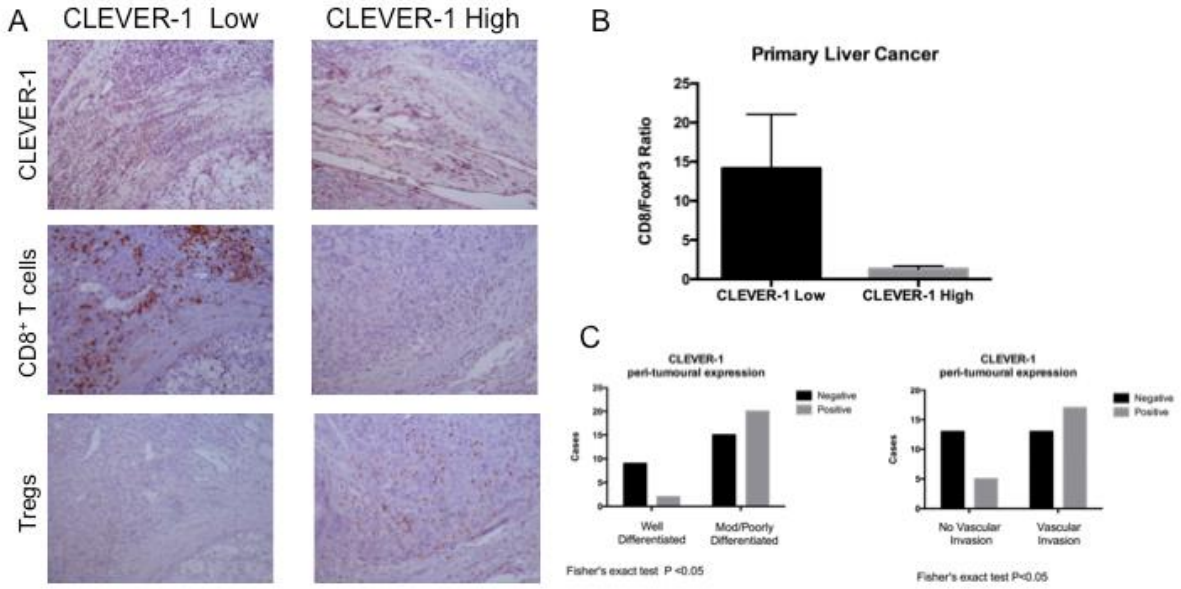

Figure 2: CLEVER-1 expression in liver cancer.

(A) Immunohistochemical staining of serial sections from primary liver cancer samples for CLEVER-1, CD8 T cells and FoxP3 positive regulatory T cells. (B) Quantification of CD8/FoxP3 ratios from CLEVER-1 low and CLEVER-1 high tumours. (C) Correlation of tumour differentiation and microvascular invasion with CLEVER-1 expression in primary liver cancer.

Preclinical studies have demonstrated that CLEVER-1 supports tumour growth and metastasis formation. Both *in vitro* and *in vivo* studies suggest that therapeutic inhibition of CLEVER-1 blocks the migration of immunosuppressive Tregs and converts immunosuppressive M2 macrophages to immunostimulatory M1 macrophages that support IFNγ production. In several preclinical tumour models, this results in tumour cell apoptosis, reduced tumour growth and suppressed metastasis formation. The aim of this trial is to investigate whether FP-1305 can safely be administered to cancer patients.

2.3.1 Safety in Non-Human Primates

The PK, pharmacodynamic (PD), and safety of FP-1305 has been studied only in non-human primates (cynomolgus monkeys) because FP-1305 binds to cynomolgus monkey CLEVER-1 but not to rodent CLEVER-1. The binding affinity is very similar compared to the human CLEVER-1. Thus, the cynomolgus monkey is a highly relevant species for toxicity analysis. The toxicity of FP-1305 has been tested in two studies. In both studies, the test subjects have received a single intravenous (I.V.) bolus injection of FP-1305. The doses in the first (pilot) study were 3, 10 and 30 mg/kg. No relevant changes were observed at clinical observations, body weights, electrocardiography (ECG) examinations, haematology, serum chemistry and at necropsy. In the second study, the administered single doses were 3, 30 and 100 mg/kg. No relevant changes were observed at clinical observations, body weights, ECG examinations, haematology, serum chemistry and at necropsy.

2.3.2 Pharmacokinetics in Non-Human Primates

After I.V. administration of FP-1305, mean ± SD C0 (5 minutes post-dosing) was 67.05± 6.1, 731±72.6 and 2755± 250.2 µg/mL following 3, 30 and 100 mg/kg single dosing, respectively. The corresponding AUC∞ were 677.2± 95.8, 20683± 3241.6 and 144000± 20174.2 µg·h/mL, respectively. The terminal half-life of FP-1305 was 18.3± 7.8, 13.7± 7.75 and 23.9± 5.9 hours at 3,

30 and 100 mg/kg, respectively. The compound was characterized by low serum clearance and limited volume of distribution.

Before dosing of FP-1305, the percentage of FP-1305 positive CD14+ monocytes in cynomolgus circulation ranged from 50 to 80%. After dosing, the proportion of FP-1305 positive CD14+ monocytes was clearly reduced in all doses indicating that FP-1305 occupies CLEVER-1 in those cells. The number of CD14+ monocytes remained unchanged.

2.3.3 Summary of Pre-Clinical Observations

- CLEVER-1 is present in human and cancer associated lymphatics.
- HEV-like vessels in inflammation and cancer express CLEVER-1.
- CLEVER-1 mediates endothelial transcytosis of immune and tumour cells.
- No clear autoimmune or other phenotype develops in anti-CLEVER-1 treated mice.
- Blocking of CLEVER-1 induces IFN-γ production in antigen specific immune response.
- Cancer progression and metastasis require host CLEVER-1 expression
- Function-blocking antibody against mouse CLEVER-1 has anti-tumour activity
- FP-1305 does not provoke significant adverse events in non-human primates after single-dose I.V. administration at the dose level 100 mg/kg

2.4 Clinical Experience of FP-1305

FP-1305 has not been studied previously in human. This is a first-in-human trial.

2.4.1 Clinical Experience of Macrophage Targeting Agents

Several molecules targeting macrophages (CSF1R or colony stimulating factor 1 antibodies, or small inhibitory molecules against CSF1R) are in development. The frequency of serious adverse events related to these compounds is low. Emactuzumab (RG7155) is a monoclonal antibody that inhibits CSF1R activation. Based on a safety evaluation of 80 patients treated with emactuzumab for solid tumours, one patient experienced a Grade 4 adverse event (a cerebrovascular accident), one patient had Grade 3 Klebsiella sepsis, and one Grade 3 dermatomyositis (Gomez-Roca et al. 2015). AMG 820 is another CSF1R targeting antibody. Twenty-five patients received AMG 820 during a dose escalation study. No serious or fatal treatment-related adverse events were observed (Papadopoulos et al. 2017). Common treatment related adverse events were peripheral/facial/periorbital oedema, asthenia, pruritus, fatigue, decreased appetite, nausea, rash, pyrexia, and diarrhoea (Papadopoulos et al. 2017; Gomez-Roca et al. 2015). Grade 3 asthenia and fatigue were observed in 3 and 1 out of the 80 evaluable patients, respectively, who were treated with emactuzumab (Gomez-Roca et al. 2015). Two patients developed cutaneous and mucosal lesions consistent with subacute lupus erythematosus, but no visceral involvement specific to systemic lupus disease. These patients were treated with hydroxychloroquine and low-dose steroids, which led to rapid clinical improvement. The clinical signs and symptoms resolved without late sequelae in both patients (Cassier et al. 2015).

2.5 Rationale for Tumour Types

The overall rationale for selecting study subjects with certain tumours is based on the non-clinical research. Based on immunohistochemistry analysis, the included tumour types contain macrophages that express CLEVER-1 on their surface. In addition, surrogate antibody targeting mouse CLEVER-1 has demonstrated robust anti-tumour activity for example in a melanoma model.

2.5.1 Hepatobiliary Cancers

Hepatobiliary tumours comprise several major global cancers including hepatocellular (HCC) and biliary tract cancers (Kabbach et al. 2015). Biliary tract cancers are sub-classified into intrahepatic cholangiocarcinoma, originating from the biliary tree within the liver, and extrahepatic cholangiocarcinoma, outside the liver parenchyma; the latter is further subdivided into perihilar cholangiocarcinoma and distal cholangiocarcinoma, with a frequency of 10%–20% intrahepatic, 50% perihilar and 30%–40% extrahepatic cholangiocarcinoma (Valle et al. 2016).

Despite advances in surgical techniques and chemotherapeutic agents, the overall survival in these patients remains extremely poor. Statistics from Cancer Research UK demonstrate that since the 1970s liver cancer rates have more than tripled (236% increase) in Great Britain and a study from two major UK centres demonstrate an overall 5-year survival of less than 20% for these patients (Than et al. 2017).

The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used and encompasses all HCC patients. The system identifies those patients with early HCC who may benefit from curative therapies (stage 0 and A), those at intermediate (stage B) or advanced stage (stage C) who may benefit from palliative treatments and those with a very poor life expectancy (stage D). Median survival without therapy is >36 months for stage 0 and A, 16 months for stage B, 4–8 months for stage C and <4 months for stage D. Over 50% of patients with moderately or poorly differentiated HCC are CLEVER-1 positive and this positivity correlates with low CD8/FoxP3 ratio (see Figure 2 in Section 2.3)

Sorafenib is the standard systemic therapy for patients with advanced HCC and well- preserved liver function (BCLC stage C) and those with intermediate-stage HCC who progress following transarterial chemoembolization. In case of disease progression or intolerance to sorafenib, best supportive care or inclusion into clinical trials for new therapeutic agents are the only options for patients. Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen or somatostatin analogues are not recommended for the clinical management of HCC patients (Verslype et al. 2012). Thus, there is a high unmet medical need for HCC patients.

Biliary tract cancers comprise <1% of all human cancers and ~10–15% of all primary liver cancers. The preferred treatment is surgery. Systemic chemotherapy, consisting of gemcitabine and cisplatin, is the standard of treatment for advanced biliary tract cancers. There is no established second-line systemic therapy following progression after first-line treatment and patients should be encouraged to participate in clinical trials (Valle et al. 2016).

2.5.2 Pancreatic Cancer

Patients with pancreatic cancer succumb to the disease. Metastases are frequent even when the primary tumour is small, hampering the efficacy of local treatments including surgery and chemoradiotherapy. The available systemic treatments also have limited efficacy. Gemcitabine combined with another agents, such as nab-paclitaxel or S1, or FOLFIRINOX, are often used as the first-line treatment for advanced disease (Cascinu et al. 2010), but the response rates are relatively low and the responses usually short. Moreover, conventional chemotherapy frequently has adverse effects, and not all patients are candidates for chemotherapy due to poor performance status or other reasons. Therefore, there is an unmet need for more effective and well tolerated systemic therapies for patients with pancreatic cancer.

Thus far, results with the current immunotherapies have mostly remained unimpressive in pancreatic cancer. Most pancreatic cancers often do not respond to PD-1 therapy even though cancer mutational rate is often high. This may not be surprising, since pancreatic cancer is characterized with a highly immunosuppressive microenvironment with a high macrophage content. Many patients with pancreatic cancer whose disease progresses on the first-line treatment are candidates for a clinical trial since the efficacy of the currently available second-line systemic treatments remains limited.

The immune microenvironment in pancreatic cancer has also been shown to significantly correlate with tumour stage and prognosis. Advanced and aggressive pancreatic cancers are associated with high levels of regulatory T cells and TAMs (Ikemoto et al. 2006; Ino et al. 2013) many of which are CLEVER-1 positive (Faron data on file). These cancers have been shown to be characterised by a disproportionally high level of Th2 cells (pro-tumour) in comparison to Th1 cells (anti-tumour) cells (Gabitass et al. 2011). Furthermore, preclinical studies have demonstrated a major role for tumour associated macrophages in the progression and metastases of pancreatic ductal adenocarcinomas (Nielsen et al. 2016).

2.5.3 Colorectal Adenocarcinoma

The majority of patients with colorectal cancer have metastatic disease that initially is not suitable for potentially curative resection. The backbone of first-line palliative chemotherapy consists of a fluoropyrimidine (I.V. 5-fluorouracil (5-FU) or the oral capecitabine) in various combinations and schedules. Combination chemotherapy with 5-FU/Leucovorin/oxaliplatin (FOLFOX) or 5-FU/Leucovorin/irinotecan (FOLFIRI) provides higher response rates, longer progression-free survival and better survival than 5-FU/Leucovorin alone. Biological agents against vascular endothelial growth factor and against the epidermal growth factor receptor in combination with chemotherapy further improve the outcome of metastatic colorectal cancer, but also increase the rate of adverse reactions. Epidermal growth factor receptor targeting agents may only be used when patients are tested to have normal (wildtype) RAS genes in expanded gene analysis. The treatment of metastatic colorectal cancer should be approached as a continuum of care in the strategic choice of a regimen or sequence in the different lines. Regorafenib is to be considered a standard option in pre-treated patients. PD-1 blockage in second- or third-line therapy could be considered as a treatment option but only in patients with metastatic deoxyribonucleic acid (DNA) mismatch repair (MMR-deficient) colorectal cancer. The survival of colorectal cancer patients is longer if patients can be exposed to all of the available cytotoxic agents. Therefore, different scenarios of colorectal cancer treatment include even four to five lines of therapy. The choice of the combinations in different lines will depend on the molecular characterisation of the tumour, the goal of treatment, the toxicity of the agents and the knowledge of mutation status of the tumour. Although the outcome of patients with metastatic colorectal cancer has clearly improved during recent years, the median survival is reaching only 30 months in clinical trials. Colorectal adenocarcinoma contains macrophages that are positive for CLEVER-1. In stage IV disease this positivity correlated with poor survival (Algars et al. 2012)

2.5.4 Ovarian Cancer

High grade (type II) ovarian carcinomas are biologically aggressive tumours that do not have a recognised precursor lesion and may arise de novo from the coelomic epithelium. The prototype of type II ovarian cancer is serous carcinoma. Included in this group are high-grade transitional carcinomas, malignant mixed mesodermal tumours, and undifferentiated carcinomas. Type II tumours show considerable genetic instability and TP53 mutations. Hereditary cancers with breast cancer gene (BRCA) 1 or 2 mutations belong to type II tumours (Vang et al. 2009). Practically all macrophages in type II ovarian cancer are CLEVER-1 positive (Faron data on file). There are limited

treatment options for patients with platinum/taxane-refractory disease, as salvage chemotherapy with either platinum-based treatments or other drugs (including topotecan, docetaxel, oral etoposide, liposome encapsulated doxorubicin, gemcitabine, ifosfamide and hexamethylmelamine) produce a modest response rate that is around 10%. Some targeted agents, including bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors, such as 41laparib and rucaparib, have been approved for the treatment of advanced ovarian cancer, the PARP inhibitors showing efficacy mainly in patients with BRCA mutation. Yet, cure from advanced (stage IV) epithelial ovarian cancer that is refractory to platinum agents is rare. Patients with such a disease and a good performance status, and who are motivated to receive further treatment, may be considered for experimental trials with new drugs (Colombo et al. 2010). Many ovarian cancers are CLEVER-1 positive (Faron data on file).

2.5.5 Cutaneous Melanoma

Systemic treatment of advanced cutaneous melanoma has recently substantially improved after the introduction of BRAF inhibitors and immunotherapy with checkpoint inhibitors. Responses to these novel agents are frequent. A subset of patients with advanced cutaneous melanoma treated with checkpoint inhibitors survive for at least 5 years after starting the therapy, which is an important advance in the treatment of this disease that is notoriously resistant to most conventional chemotherapy agents.

There are, however, few effective treatment options for patients with immunotherapy resistant cutaneous melanoma. The response rate for CTLA-4 blockage in treatment naïve patients is around 10%, and the responses with this therapy after the failure of anti-PD-1 treatment are infrequent. Cytotoxic chemotherapy has only very modest efficacy with about 10% response rates in advanced cutaneous melanoma. BRAF-inhibitor therapy alone or in combination with mitogen-activated protein kinase inhibitor is an effective option for patients advanced cutaneous melanoma, if the patient has a cutaneous melanoma with BRAF V600 mutation, but drug resistance will usually emerge. Patients with cutaneous melanoma resistant to PD-1 targeting agents often have high serum lactate dehydrogenase (LDH) levels, which may indicate a low pH in the tumour tissue.

Thus, most patients whose advanced cutaneous melanoma does not respond to immunotherapy, or whose disease progresses on immunotherapy, have few viable treatment options, and may have an immunosuppressive tumour environment with increased CLEVER-1 expression. In addition, mouse anti-CLEVER-1 antibody demonstrates robust anti-tumour activity in B16 melanoma model (Karikoski et al. 2014).

2.5.6 Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, representing ~85% of ocular melanomas. Cutaneous and uveal melanomas are biologically distinct. Uveal melanoma is composed of a number of chromosomal abnormalities and somatic gene alterations. Despite the development of effective local therapies, 5-year survival rates (~80%) have not changed in the past three decades and up to 50% of patients develop metastases. There are no effective adjuvant systemic therapies nor systemic therapies against metastatic disease and the NCCN (National Comprehensive Cancer Network) guideline first recommendation for metastatic disease is a clinical trial. One-year survival of patients with metastatic disease is reported to be 15%, with reported median survival ranging from 4 to 15 months (Carvajal et al. 2017). The risk of death among uveal melanoma patients is significantly higher if CLEVER-1 expression is high in comparison to patients with low CLEVER-1 expression (Goldman et al. 2018).

2.5.7 Gastric adenocarcinoma

Surgical resection of gastric cancer (including GE junction), specifically at early stages, is potentially curative. However, the majority of patients still relapse following perioperative chemotherapy and resection. Patients with inoperable locally advanced and/or metastatic (stage IV) disease should be considered for a systemic treatment (chemotherapy). Doublet combinations of platinum and fluoropyrimidines are generally used and triplet regimens containing anthracycline, platinum and fluoropyrimidine may improve efficacy. Second-line treatment is associated with proven improvements in overall survival and quality of life compared with best supportive care in patients with adequate performance status. In human epidermal growth factor receptor 2-positive gastric cancer trastuzumab in combination with capecitabine or fluorouracil and cisplatin is a standard first line treatment. However, the median overall survival of metastatic gastric adenocarcinoma is approximately 12 months (Smyth et al. 2016).

Immune checkpoint inhibitors demonstrate some activity in unresectable advanced or recurrent gastric or esophago-gastric junction cancer patients refractory to or intolerant to two or more prior chemotherapy regimens. However, the response rates in later line settings are close to 10% and a median overall survival remains poor (approximately 5 months) even though the responders may have long term benefit from the therapy (Kang et al. 2017). Thus, prognosis remains poor in presence of metastatic disease and new treatment approaches are desirable. Based on gene expression analysis, high CLEVER-1 expression correlates with poor survival in gastric adenocarcinoma (Goldman et al. 2018).

2.5.8 Estrogen receptor (ER)+ breast cancer

Advanced breast cancer comprises both locally advanced breast cancer and metastatic breast cancer. The preferred treatment for metastatic ER+ (luminal) breast cancer is endocrine therapy even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. Adequate ovarian function suppression or ablation is crucial in the treatment of pre-menopausal patients with ER+ advanced breast cancer. The addition of a cyclin dependent kinase 4/6 inhibitor to an aromatase inhibitor is recommended to aromatase inhibitor naïve patients or patients previously treated with endocrine therapy in adjuvant setting and not considered resistant to the treatment. Systemic chemotherapy with anthracycline- or taxane-based regimens is also reasonable option. These agents may be used in combinations or sequential single agents. Optimal sequence of all these treatments and best management for patients who progressed during or less than 1 year after adjuvant is still unknown. Despite all the treatment options, metastatic breast cancer remains virtually an incurable disease with a median overall survival of approximately 3 years. 5-year survival is only approximately 25%. The European School of Oncology–European Society of Medical Oncology International Consensus Guidelines recommends inclusion of patients in well-designed, prospective, independent trials. High CLEVER-1 expression is associated with poor survival in ER+ breast cancer (Goldman et al. 2018).

2.5.9 Anaplastic thyroid cancer

Anaplastic thyroid cancer (ATC) is an aggressive form of thyroid cancer with a mortality approaching 100%. It is rare and accounts for about 2% of all thyroid cancers. Patients are diagnosed based on clinical symptoms. Patients with the disease present with extensive local invasion. Distant metastases are found at initial disease presentation in 15% to 50% of patients. No curative therapy exists for ATC. Surgery, external beam radiotherapy or chemoradiotherapy are options for local disease control. For metastatic disease, systemic therapies include combinations of paclitaxel and carboplatin or docetaxel and doxorubicin. Paclitaxel or doxorubicin may also be used alone. However, the

median survival from ATC diagnosis is about five months. The one-year survival rate is about 20% (Smallridge et al. 2012).

2.6 Trial Rationale

The trial will be conducted according to the trial protocol, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice (GCP) and applicable regulations.

2.6.1 Justification for Trial Subject Populations

Preclinical studies have demonstrated that CLEVER-1 supports tumour growth and metastasis formation. Both *in vitro* and *in vivo* studies suggest that therapeutic inhibition of CLEVER-1 blocks the migration of immunosuppressive Tregs and converts immunosuppressive M2 macrophages to immunostimulatory M1 macrophages that present antigens to T-cells and support IFN-γ production. In several preclinical tumour models, including melanoma, this results in tumour cell apoptosis, reduced tumour growth and suppressed metastasis formation. As stated earlier, the patients with advanced cutaneous melanoma, uveal melanoma, cholangiocarcinoma, gallbladder cancer, ER+ breast, gastric, ovarian, pancreatic, colorectal, liver or anaplastic thyroid cancer who have exhausted all licenced therapeutic options will die due to their disease. Based on our existing data CLEVER-1 is expressed in these tumour types. Inhibition of CLEVER-1 with FP-1305 may have an anti-tumour effect in these patients.

2.6.2 Justification for Design

The proposed trial design enables a flexible approach to identify a safe and tolerable dose which has a biological effect and to expand the cohorts of different tumour types after the dose has been selected. Analysis of the primary efficacy in the expansion cohorts early enough with sufficient statistical power allows for a rapid adaptation of the protocol in order to focus on the tumour types in which the treatment demonstrates the most promising activity. Subject safety will be closely monitored after the first infusion and regularly throughout the trial (see Section 8.2). The highest dose that can be tolerated (maximum tolerated dose (MTD)) will be first determined using an efficient, adaptive dose-finding design, a modified time-to-event continual reassessment method (TITE-CRM), which allows for more accurate determination of the MTD and shorter trial duration than conventional dose-finding designs (Cheung and Chappell 2000). This initial design allows a simple and rapid escalation scheme (whilst still ensuring safety) in the absence of DLT.

Due to its mechanism of action it is likely that a therapeutic response with FP-1305 will require repeated dosing. Therefore, the trial design is based on repeated infusions in three-week intervals. There is a minimum waiting period of three weeks prior to the recruitment of the next study subject at the same dose level. Both recruited subjects dosed at the first dose level will be observed for a minimum of three weeks for DLT before dose will be escalated into next level.

More subjects may be allocated during Part I to MTD or any dose below it to obtain necessary information for proper dose selection for Part II. It is estimated that a total of 30 subjects will be accrued for the MTD determination during Part I. Detailed PK and PD data will be collected to further inform the optimal dose selection for the expansion cohorts.

Early termination of an individual cohort in case there is no efficacy ensures that subjects are not enrolled into the trial if the treatment is not efficacious. The subject will continue the trial treatment until the participation in the trial is no longer considered to be in the best interest of the subject (as

judged by the investigator), or until any of the other discontinuation rules is met (see 10.4). If a subject is treated with a dose that does not show activity, the dose will be escalated when the dose level above it has been shown to be safe and PK data from Cycle 4 has been collected from the initial dose level.

2.6.3 Justification for Initial Dose, Dosing Interval and Dose Escalation

The selection of the initial dose was based on the nonclinical safety findings, receptor occupancy at the 3 mg/kg dose, the affinity of FP-1305 to CLEVER-1 and the binding of FP-1305 to CD14+ monocytes derived from healthy volunteers *in vitro*. No relevant toxicities in non-human primates were observed after 100 mg/kg dosing. Thus, there is over a 300-fold safety margin with the initial 0.3 mg/kg dose in humans. However, CLEVER-1 on monocytes should already be occupied at the 0.3 mg/kg dose level, based on the receptor occupancy and *in vitro* monocyte binding.
Based on the FP-1305 pharmacokinetics in non-human primates, the 3-week dosing interval (Q3W) and the dose escalation scheme is considered appropriate.

In addition to the Q3W dosing, Protocol Addendum introduces once in two weeks (Q2W) and once in week (Q1W) dosing schemes to be investigated in the Part II of the study. The scientific rationale for investigating more frequent dosing (Q2W and Q1W) is based on Part I PK and receptor occupancy of the CLEVER-1 (refer to Investigator's Brochure). This Protocol Addendum may not be submitted to all countries participating in the study. The countries selected to participate to enrol patients under the Protocol Addendum will be formally notified, and the Protocol Addendum will be submitted with the main protocol for Competent Authority and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval.

During Part II, additional dose levels are tested to investigate tolerability and safety in a broader dose range, and to receive additional data about the PK, RO and preliminary efficacy. The selected doses are 30 mg/kg and 100 mg/kg; an intermediate dose of 45 mg/kg may be included if deemed necessary based on accumulated data. The scientific rationale for investigating higher doses (30 mg/kg-100 mg/kg) is based on the cumulative study data, e.g. PK (relatively fast $T_{1/2}$) and RO (transient) of the CLEVER-1 at dose levels of 0.1 – 10 mg/kg (refer to Investigator's Brochure), and accumulated safety data indicating good tolerability of the IMP and no DLT events registered.

Inclusion of multiple distinct cancer types to the first cohort of ten subjects at a new dose level is possible, justified by allowing the investigation of the safety of the dose level in a wider population than just one particular cancer type in Part II. However, if deemed necessary, multiple cohorts with distinct cancer types may be selected to be explored at a dose level. This approach is justified by allowing the investigation of the safety and preliminary efficacy properly in Part II, as distinct cancer types may respond differently to the treatment.

3 OBJECTIVES

3.1 Primary Objective for Part I

- To determine the safety, tolerability and recommended dose of FP-1305 for Part II and III in subjects with advanced (inoperable or metastatic) hepatobiliary, pancreatic, colorectal or ovarian cancer or melanoma subjects without standard treatment options

3.2 Secondary Objectives for Part I

- To characterize the PK profile of a single dose of FP-1305 after the first dosing

- To characterize the PK profile of FP-1305 during repeated dosing
- To assess the host immune response to FP-1305 (immunogenicity)
- To assess the preliminary efficacy of FP-1305 monotherapy with the ORR and irORR in each cohort of different tumour type

3.3 Exploratory Objectives for Part I

- To determine CLEVER-1 positivity in each tumour type
- To characterize the receptor occupancy of FP-1305 on circulating monocytes
- To explore potential predictive markers associated with FP-1305 clinical activity
- To explore potential markers associated with FP-1305 clinical activity during the treatment
- To assess cytokine and chemokine concentrations (consisting of a panel of cytokines and chemokines) in the peripheral blood prior to FP-1305 treatment and during the FP-1305 treatment up to Cycle 4
- To measure the immune cell profile in circulation
- To assess if treatment elicits a change in LDH, LDL and oxLDL, C-reactive protein (CRP), Cancer antigen (CA)-125 (ovarian cancer (OC) subjects), CA19-9 (PDAC, cholangiocarcinoma subjects), alpha fetoprotein (AFP) (HCC subjects), Carcinoembryonic antigen (CEA) (colorectal adenocarcinoma (CRC) subjects) levels or other relevant markers pre- and post-treatment
- To investigate the duration of response in the subject group that has a complete or partial response
- To assess progression free survival in subjects who receive at least 1 dose of FP-1305
- To assess the overall survival in subjects who receive at least 1 dose of FP-1305

3.4 Primary Objective for Part II

- To determine the safety, tolerability and preliminary efficacy of FP-1305 monotherapy with the ORR, CBR and irORR in distinct expansion groups of subjects with advanced (inoperable or metastatic) solid tumours of the selected tumour types

3.5 Secondary Objectives for Part II

- To determine CLEVER-1 positivity in each tumour type
- To characterize the PK profile of a single dose of FP-1305 after the first dosing for each cohort of different tumour type
- To characterize the PK profile of FP-1305 during repeated dosing in each cohort of different tumour type
- To assess the host immune response to FP-1305 (immunogenicity) in each tumour type
- To explore potential predictive markers associated with FP-1305 clinical activity as determined by ORR, CBR and irORR
- To investigate the duration of response in the subject group that has a complete or partial response, or SD

3.6 Exploratory Objectives for Part II

- To assess the amount of soluble CLEVER-1 (sCLEVER-1) in the patients prior to treatment
- To characterize the receptor occupancy of FP-1305 on sCLEVER-1 and/or on circulating monocytes at different dose levels/dosing frequencies
- To assess the CBR of trial subjects according to the number of CD8 positive cells within the tumour stroma

- To assess progression free survival in trial subjects who receive at least 1 dose of FP-1305
- To assess the overall survival in trial subjects who receive at least 1 dose of FP-1305
- To measure cytokine and chemokine concentration in peripheral blood
- To measure the immune cell profile in circulation
- To assess if treatment elicits a change in LDH, LDL and oxLDL, CRP, CA-125 (OC subjects), CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects), AFP (HCC subjects), CEA (CRC, ER+ BC, gastric adenocarcinoma subjects), CA-15-3 (ER+ BC subjects) levels or other relevant markers pre- and post-treatment

3.7 Primary Objective for Part III

- To assess the ORR, CBR and irORR in distinct expansion groups of subjects with advanced solid tumours in CLEVER-1 positive subjects from selected tumour types at a selected dose

3.8 Secondary Objectives for Part III

- To characterize population PK of FP-1305 in each selected tumour type during repeated dosing
- To assess the host immune response to FP-1305 (immunogenicity)
- To assess the duration of response in distinct expansion groups of subjects with advanced solid tumours in CLEVER-1 positive subjects from selected tumour types at a selected dose
- To assess progression free survival in subjects who receive at least 1 dose of FP-1305
- To assess the overall survival in subjects who receive at least 1 dose of FP-1305
- To determine the safety and tolerability of FP-1305 during repeated dosing in each tumour type at a selected dose

3.9 Exploratory Objectives for Part III

- To measure cytokine concentration in the peripheral blood
- To measure immune cell profile in circulation
- To assess if treatment elicits a change in LDH, and oxLDL, CRP, CA-125 (OC subjects), CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects), AFP (HCC subjects), CEA (CRC, ER+ BC, gastric adenocarcinoma subjects), CA-15-3 (ER+ BC subjects) levels or other relevant markers pre- and post-treatment

3.10 Outcome Measures

Part I

Primary outcome measure

- Tolerable dose(s) will be determined by the TITE-CRM based on the occurrence/non-occurrence of dose limiting toxicities in the trial subjects according to definitions in Section 4.1.

Secondary outcome measures

- The PK profile of a single dose (during Cycle 1) and repeated doses (during Cycles 1-5) of FP-1305 will be determined by repeated measurements of the drug concentration in the circulation. Peak concentration (Cmax), trough concentration (Cmin), AUC, clearance, volume of distribution, and terminal half-life (t1/2) for each dose level will be determined.
- Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up.

- The ORR to the treatment will be determined by tumour imaging according to RECIST 1.1. The CBR is the proportion of subjects that have a complete response, partial response, or stable disease. The irORR will also be calculated.

Exploratory outcome measures

- CLEVER-1 on circulating monocytes will be determined by flow cytometry. The proportion of circulating CD14+ monocytes binding labelled FP-1305 prior to treatment and their mean fluorescence intensity (MFI) will be used to define CLEVER-1 positivity. CLEVER-1 in tumour samples (if available) prior to treatment will be identified with immunohistochemistry and reported as positive cells / mm^2 of sample. The MFI of CLEVER-1 positive cells will be correlated to the number of CLEVER-1 positive cells in the tumour sample if the number is available.
- The proportion of circulating monocytes binding labelled FP-1305 and another CLEVER-1 binding antibody prior to and during the treatment at selected time points and their MFI will be reported.
- Potential predictive genetic, cellular and other markers will be associated with FP-1305 clinical activity as determined by ORR and irORR. This includes but is not limited to the correlation of response and immune cell profile, cytokine/chemokine profile and the proportion of CLEVER-1-positive monocytes, CD4, CD8, their ratio and regulatory T-cells in the circulation and in tumour specimens prior to treatment and in circulation during the first cycle of treatment.
- The proportion of lymphocyte subsets (CD4, CD8, their ratio, NK-cells, B-cells and regulatory T-cells, and macrophage HLA expression and myeloid derived suppressor cell populations in circulation will be analysed at given time points with flow cytometry and plotted against the scheduled sampling time. The level of circulating cytokines and chemokines (including but not necessarily limited to IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8/CXCL8, IL-10, IL-12p70, IL-13 and TNF alpha, IP-10/CXCL10, Eotaxin/CCL11, MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4) will be analysed by multiplex assays prior to and during the treatment. Aggregated data (mean and median) from each dose level will be presented using descriptive statistics.
- LDH, LDL and oxLDL, CRP, CA-125 (OC subjects), CA19-9 (PDAC, cholangiocarcinoma subjects), CEA (CRC subjects) and AFP (HCC subjects) levels prior to and during the treatment will be measured from blood.
- The ORR to the treatment will be determined by tumour imaging according to RECIST 1.1. The CBR is the proportion of subjects that have a CR, PR, or SD. The irORR will also be calculated. Results from each tumour type will be reported separately.
- The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout.
- Progression free survival as the time from subject allocation into the trial until documented disease progression according to RECIST 1.1 or death will be measured in the population that has been dosed at least once.
- Overall survival is defined as the time from subject allocation into the trial until death from any cause and will be measured in the population that has been dosed at least once. Data will be censored on the last documented data that the subject has been alive.

Part II

Primary outcome measures

- Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are collected, graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data. Tolerability of new dose(s) will be determined based on the occurrence/non-occurrence of DLT during 28 days following the first dose of FP-1305 in subjects evaluable for DLT assessment in Part II.
- The response (ORR, CBR, and irORR separately) to the treatment will be determined by tumour imaging according to RECIST 1.1 based on images obtained by Cycle 7. Results from each tumour type, dose level and dosing frequency will be reported separately.

Secondary outcome measures

- The PK profile of a single dose (during Cycle 1) and repeated doses (during Cycles 2-5) of FP-1305 will be determined by repeated measurements of the drug concentration in the circulation. Peak concentration (Cmax), trough concentration (Cmin), AUC, clearance, volume of distribution, and terminal half-life (t1/2) for each dose level will be determined. Results from each tumour type will be reported separately.
- Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up. Results from each tumour type will be reported separately.
- Potential genetic, cellular and other predictive markers will be associated with FP-1305 clinical activity as determined by ORR, CBR and irORR. This includes but is not limited to the correlation of response and immune cell profile, cytokine/chemokine profile and the proportion of CLEVER-1-positive monocytes, CD4, CD8, their ratio and regulatory T-cells in the circulation and in tumour specimens prior to treatment and in circulation during the first cycle of treatment.
- The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout.
- Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data.

Exploratory outcome measures

- CLEVER-1 on circulating monocytes will be determined by flow cytometry. The proportion of circulating CD14+ monocytes binding labelled FP-1305 prior to treatment and their MFI will be used to define CLEVER-1 positivity. CLEVER-1 in tumour samples (if available) prior to treatment will be identified with immunohistochemistry and reported as positive cells / mm2 of sample. The MFI of CLEVER-1 positive cells will be correlated to the number of CLEVER-1 positive cells in the tumour sample if the number is available.
- The proportion of circulating monocytes binding labelled FP-1305 and another CLEVER-1 binding antibody prior to and during the treatment at selected time points and their MFI will be reported.
- sCLEVER-1 and its blockage will be determined by measuring the amount of sCLEVER-1 with immunoassay prior to treatment and during the treatment.
- CD8 positive cells within the tumour stroma prior to treatment will be identified with immunohistochemistry and reported as positive cells / mm2 of sample. The subjects will be

grouped according to response (CR/PR/SD/Progressive disease) and the mean number of CD8 positive cells according to each group will be reported.

- Progression free survival as the time from subject allocation into the trial until documented disease progression according to RECIST 1.1 or death will be measured in the population that has been dosed at least once.
- Overall survival is defined as the time from subject allocation into the trial until death from any cause and will be measured in the population that has been dosed at least once. Data will be censored on the last documented data that the subject has been alive.
- The proportion of lymphocyte subsets (CD4, CD8, their ratio, NK-cells, B-cells and regulatory T-cells), and possibly macrophage HLA expression and myeloid derived suppressor cell populations in circulation will be analysed at given time points with flow cytometry and plotted against the scheduled sampling time. The level of circulating cytokines and chemokines (including but not necessarily limited to IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8/CXCL8, IL-10, IL-12p70, IL-13 and TNF alpha, IP-10/CXCL10, Eotaxin/CCL11, MCP-1/CCL2, MIP-1α /CCL3, MIP-1β/CCL4) will be analysed by multiplex assays prior to and during the treatment.
- LDH, LDL, oxLDL, and CRP, as well as the following tumour specific markers CA-125 (OC subjects), CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects), CEA (CRC, ER+ BC, gastric adenocarcinoma subjects), AFP (HCC subjects), CA-15-3 (ER+ BC subjects) levels prior to and during the treatment will be measured from blood.

Part III

Primary outcome measure

- The response (ORR CBR and irORR separately) to the treatment will be determined by tumour imaging according to RECIST 1.1 based on images obtained by Cycle 7. Results from each tumour type will be reported separately.

Secondary outcome measures

- The population PK of FP-1305 will be determined by measurements of the drug concentration in the circulation between Cycles 1 and 5. Results from each tumour type will be reported separately.
- Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up. Results from each tumour type will be reported separately.
- The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout.
- Progression free survival as the time from subject allocation into the trial until documented disease progression according to RECIST 1.1 or death will be measured in the population that has been dosed at least once.
- Overall survival is defined as the time from subject allocation into the trial until death from any cause and will be measured in the population that has been dosed at least once. Data will be censored on the last documented data that the subject has been alive.
- Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data

Exploratory outcome measures

- The proportion of lymphocyte subsets (CD4, CD8, their ratio, NK-cells, B-cells and regulatory T-cells), and macrophage HLA expression and myeloid derived suppressor cell populations in circulation will be analysed at given time points with flow cytometry and plotted against the scheduled sampling time. The level of circulating cytokines and chemokines (including but not necessarily limited to IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8/CXCL8, IL-10, IL-12p70, IL-13 and TNF alpha, IP-10/CXCL10, Eotaxin/CCL11, MCP-1/CCL2, MIP-1α /CCL3, MIP-1β/CCL4) will be analysed by multiplex assays prior to and during the treatment.
- LDH, LDL, oxLDL, and CRP, as well as the following tumour specific markers CA-125 (OC subjects), CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects), CEA (CRC, ER+ BC, gastric adenocarcinoma subjects), AFP (HCC subjects) and CA-15-3 (ER+ BC subjects) levels prior to and during the treatment will be measured from blood.

4 TRIAL DESIGN

This is a prospective, three-part (see Figure 1) open label, Phase I/II dose-finding and separate cohorts expansion trial to determine the safety, tolerability and efficacy of CLEVER-1 antibody FP-1305 in subjects with cutaneous melanoma, pancreatic ductal adenocarcinoma, ovarian cancer, colorectal adenocarcinoma, hepatocellular carcinoma, gallbladder cancer, cholangiocarcinoma, uveal melanoma, gastric (including GE junction) adenocarcinoma, ER+ breast cancer and anaplastic thyroid cancer. The enrolment period for Part I lasted for 13 months. It is estimated that the enrolment period for both Part II and III would be 24 months for either part. For each subject, the trial will consist of a screening period (maximum 28 days), treatment phase with FP-1305 (one year with potential to continue longer), and a post-treatment period for safety assessment (maximum 4 weeks). Survival data will be collected beyond the subject's active participation in the trial. The collection of the survival data of a subject is limited to 2 years from the first IMP dose (at 1 year and 2 years after the first IMP dose). The maximal total duration of the trial is estimated to be 6 years. In case it would be beneficial for a study subject to continue the treatment beyond one year (as judged by an investigator), the treatment can be continued within this protocol and the survival data will be collected for 1 year after the last IMP dose (see 8.7.1).

Part I of the trial will involve the identification of tolerable doses amongst four predefined doses. This will be based on the occurrence of DLTs with an acceptable (target) DLT rate of 20%. It is estimated that in total 30 subjects in 2-4 countries will be accrued from all disease groups to be investigated. The highest dose that can be tolerated based on the target (maximum tolerated dose) will first be determined using an efficient, adaptive dose-finding design, a modified time-to-event continual reassessment method (TITE-CRM), which allows for more accurate determination of the highest tolerated dose and shorter trial duration than conventional dose-finding designs. An early stopping rule will be incorporated to allow the trial to stop early or insert a lower dose if there is an unacceptable level of DLT at the lowest dose (level 0; 0.3 mg/kg). The lower reserve dose levels are 0.1 mg/kg and 0.05 mg/kg as shown in Table 4. The de-escalation reserve dose levels will be utilised if there is strong evidence to suggest that the MTD is lower than 0.3 mg/kg and may be utilised also if more data on safety, PK and/or PD markers is required for dose selection for Part II. The 20 mg/kg dose may be utilized based on MTD or receptor occupancy and other PD markers.

The decision on the number and timing of the doses via intravenous infusion was guided by nonclinical studies. The initial FP-1305 dose level (Dose Level 0; Table 4) is 0.3 mg/kg every

three weeks. For further dosing see also Table 4. The full DLT assessment period is 63 days (9 weeks) for each subject from the first dose in Part I. If a subject misses a dose during the DLT period, the period is not changed, but stays as nine weeks from the first dosing. Based on the preclinical data it is expected that the selected doses will be well-tolerated.

Table 4: Dose levels in Part I of the trial

Dose Level	Dose (mg/kg)
-2 (reserve)	0.05
-1 (reserve)	0.1
0	0.3
1	1
2	3
3	10
4 (reserve)	20

The primary objective of the Part I of the trial is to select an optimal, biologically/ immunologically active dose that will be used in Parts II and III of the trial. Additional doses 30-100 mg/kg are included to be investigated in Part II.

In Part I, the initial design of the two-stage TITE-CRM has been chosen such that subjects will be recruited in cohorts of 2. If a subject is withdrawn/discontinued for any reason or dies during Cycle 1 (i.e. within the first three weeks after the first IMP) at the first level (Level 0), the withdrawn/discontinued subject needs to be replaced and a new subject will be enrolled to the same dose level until two subjects have reached the three-week follow-up and the dose escalation to the second level may occur. Dose-escalation will occur (where possible) if no DLTs have been observed in the first two subjects, each of them with a minimum of three-week follow-up at given dose level (). In the interest of safety, a single subject will be treated first when a new dose level is to be investigated. There is a minimum waiting period of 3 weeks prior to the recruitment of the next subject at any dose level. This initial design allows a simple and rapid escalation scheme (whilst still ensuring safety) in the absence of DLT. Subjects are continually monitored for the occurrence of DLT till 9 weeks (full DLT assessment period). The accumulated information from each subject will continually be used to guide dose decisions. Once a DLT is observed, the second stage commences and the TITE-CRM model is utilised to determine the next best estimate of the MTD, taking into account all the accumulated complete (9 weeks) and partial DLT information (< 9 weeks) of the treated subjects. The model will be updated as soon as it is feasible, for instance, after 1 or 2 subjects. In the TITE-CRM paradigm, at the point of dose-update, subjects who have started treatment but have not completed their full DLT assessment and have not experienced DLT are included in the probability calculation with a weight equal to the proportion of the full DLT assessment period they have completed. For instance, Subject X who had no DLT up to 4.5 weeks will be given a weight of 4.5/9=0.5. Subjects who experienced DLT within the assessment period or complete the full assessment period are assigned full weight (Cheung et al. 2000).

Two subjects as minimum will be assessed at each dose level if no DLT occurs. The TITE-CRM will continually re-estimate the MTD during the DLT assessment period and accumulated information will be used to determine tolerable doses. Once six evaluable subjects are treated at first three dose levels for the full DLT assessment period and two subjects are treated at the fourth dose level for

minimum of three weeks, the Data Monitoring Committee (DMC) evaluates whether reserve doses are required before the dose for Part II can be selected. If deemed necessary, reserve dose(s) will be utilised. In addition, three additional subjects per dose level may be enrolled to any tested dose level to gather more data. If subjects are allocated to two or more dose levels in Part I, randomisation to the selected doses will be utilized.

The decision of using more dose levels will be made by the DMC on the basis of the data collected from the subjects. It is estimated that approximately 30 evaluable subjects in total in Part I will be enrolled. At the end of Part I, the DMC utilises the receptor occupancy, changes in immune function, PK, PD and/or ORR data to determine the dose or doses for further investigation in Part II. Further decisions about Part II dose levels can be made based on cumulative data collected throughout the study.

In addition, the DMC may also recommend to include additional subjects on certain dose levels to ensure sufficient data is available for optimal dose selection for the Part II.

Subjects with HCC may potentially exhibit decreased antibody (FP-1305) clearance, due to a possibility that the liver endothelium's lysosomal compartment is diseased. Based on investigators best decision, and consultation of Medical Monitor, the first subject enrolled with HCC during Part I or in Part II may be administered with a dose one level lower than the highest tested dose or the phase II recommended dose. In Part II the first subject with HCC and underlying liver cirrhosis may be administered one level lower than the recommended dose level for the first dose. The recommended dose should be administered from the second dose (Cycle 2) forward if no toxicity appeared. After this, additional subjects with HCC that are enrolled should be dosed at the recommended dose level, if no toxicity has appeared for the first subject with HCC during the first cycle of treatment (3 weeks) with the lower dose level.

Part II of the trial will involve expansion groups of subjects by tumour type. The following tumour types will be selected for cohort expansion after the data of the first part of the trial has been reviewed: advanced hepatocellular carcinoma, cholangiocarcinoma and gallbladder cancer, pancreatic ductal adenocarcinoma, ovarian cancer, colorectal adenocarcinoma, cutaneous melanoma, uveal melanoma, gastric adenocarcinoma (including GE junction), ER+ breast cancer and anaplastic thyroid cancer. Each cohort will contain 10 subjects in Part II (10 at each dose level with random allocation within the same dosing schema Q3W, Q2W or Q1W. In addition, new dose level(s) 30 mg/kg and possibly also 45 and 100 mg/kg that include more than one tumour type will be tested for tolerability and safety. The data from both Part I and Part II will be used to define CLEVER-1 positivity in each tumour type. In Part III, subjects will be enrolled in tumour types that have demonstrated preliminary anti-tumour activity based on the CBR. Up to a total sample size of 700 subjects in all parts will be enrolled in approximately 20-30 sites in 5-8 countries. Subjects in Part III are stratified by disease type as in Part II and may be stratified by CLEVER-1 positivity. In Part II and Part III, cohorts for a particular tumour type may be opened sequentially or not opened at all i.e., if there is a strong signal for efficacy in cutaneous melanoma, that cohort may be opened first. Each cohort of subjects with a certain tumour type will be analysed for efficacy after 10 subjects have been treated with the dose(s) selected for Part II. The decision of continuing the cohort for Part III will be based on the results obtained from this analysis supported by the statistical rule to continue the cohort. Cohorts with best efficacy signal at any dose level may be advanced to Part III. However, it may not be meaningful to advance all Part II cohorts at any dose level with a minimal and clinically not meaningful signal of efficacy into Part III.

Figure 1A displays the trial pathway including dose escalation and expansion phases. Figure 1B displays how the initial design of the TITE-CRM will work in the absence of any DLT in Part I. Once a DLT is observed, subsequent dose decisions will be made with the usage of the TITE-CRM. This will take into account all accumulated DLT information–both partial (<9 weeks) and complete (9 weeks).

In this study protocol, the study drug is administered Q3W intervals. Based on the analysis of the PK, receptor occupancy and PD during the Q3W administration, it was deemed necessary to study more frequent dosing. With Protocol Addendum, Q2W and Q1W dosing intervals are implemented into Part II and possibly also to Part III if deemed appropriate. The purpose is to investigate the tolerability, safety, PD and preliminary efficacy of more frequent dosings infusion (Q2W and Q1W). Scientific justification and details of conducting of Q2W and Q1W dosings have been presented in the FP-1305 Investigator's Brochure and Protocol Addendum, respectively

4.1 Dose Limiting Toxicity

DLT evaluable subjects include:

- Part I: All subjects
- Part II: The first three (or six if there is one DLT in the first three) subjects in the following cohorts
    - Q3W cohorts at dose levels that have not previously been tested in Part I
    - Q2W cohorts at each new dose level for the Q2W schema
    - Q1W cohorts at each new dose level for the Q1W schema
- Part III: DLT not applicable

DLT assessment period in Part II is shorter than in Part I, justified by the safety and tolerability data collected during the trial and enabling prompt dose escalation as a part of the 3+3 design of Part II.

- Part I: 63 days (9 weeks) following the first dose of FP-1305
- Part II: 28 days (4 weeks) following the first dose of FP-1305

A DLT is defined as a drug related AE ≥ Grade 3 according to NCI-CTCAE version 5.0 occurring during the DLT assessment period and related to FP-1305. The following are exceptions to the rule:

- Grade 3 infusion reactions that resolve within 8 hours from the onset of the reaction are not defined as a DLT
- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care are not defined as a DLT
- For thrombocytopenia, haemorrhage is required to qualify grade 3 toxicity as DLT; Grade 4 thrombocytopenia is DLT regardless of haemorrhage
- For neutropenia DLT is as follows,
    - Any neutropenic fever
    - Grade 3 neutropenia persisting > 5 days or Grade 4 neutropenia
- For toxicity judged to be consistent with an acute infusion-related reaction or cytokine release syndrome, DLT will be defined as follows (Sehn 2012):
    - Grade 4 drug-related AE or
    - Grade 3 drug-related AE that cannot be resolved by infusion rate reduction or interruption, or supportive care.
- An AE which, in the opinion of the Investigator, is attributed to a study subject's underlying disease will not be considered a DLT.

In addition, the following are considered DLTs (occurring during the DLT assessment period and related to FP-1305):

- Grade ≥2 ALT or AST increase accompanied with bilirubin elevation >2x ULN if baseline value was normal; >2 x baseline if baseline value was abnormal
- Dose delay of the 2nd cycle due to drug-related toxicity of >14 days

A serious adverse event (SAE) may be considered a DLT according to this section. The severity of the AEs will be codified according to the NCI-CTCAE version 5.0. If the subject has an event that meets the DLT criteria otherwise, but it is not considered to be drug related, then the reason needs to be clearly documented. The sites are requested to report the DLTs via electronic case report form (eCRF) immediately within 24 h an event meets the DLT criteria. In case the eCRF cannot be updated with the DLT (e.g. technical issue), sites are to email to Medical Monitor immediately within 24 h stating a suspected DLT has occurred. The SAE reporting according to Section 11.4 is required in any case to all events that meet the SAE criteria.

4.2 Stopping and Dose Escalation Rule(s)

4.2.1 DLT at the Initial Dose after the First Infusion (Part I)

If the first subject experiences DLT at initial dose after first infusion, the trial will be halted, and the TITE-CRM will be updated accordingly. Reserve dose levels (-1 or -2) will be used based on the new information.

4.2.2 DLTs during the DLT Assessment Period at the First Dose Level (Part I)

A repeated dosing will be initiated at the first dose with the first subject if no DLTs have been observed during the observation period. The second subject in this cohort can be dosed with the same dose after three weeks of the initial dose (Figure 1) if the first subject did not experience DLT after the first infusion.

If one subject has DLT at the initial dose level during the DLT assessment period, recruitment to any cohort will be halted and the TITE-CRM will be updated with the new information and used to guide the decisions. Subjects in any cohort may continue receiving additional repeated doses if they have not experienced DLT while on repeated dosing and their accumulated time within the DLT assessment period will be taken into account by the TITE-CRM model.

4.2.3 Predefined Dose Escalation Rules for TITE-CRM (Part I)

Dose escalation is allowed to the next level after two subjects are treated with FP-1305 without DLT even if the full DLT assessment period is not completed. Dose escalation to further dose levels is not allowed until at least two subjects have been observed for the full DLT period. For example, dose escalation can be performed from dose level 0 to dose level 1 even if the full DLT period is not completed. However, dose escalation to level 2 is not allowed until two subjects have had the full 9-week DLT assessment either on level 0 or on level 1 and two subjects on level 1 has been dosed and followed up for a minimum of three weeks after the first dose. Similarly, the dose cannot be escalated from the third (Level 2) to the fourth level (Level 3) before the full DLT period of nine weeks is reached altogether from two previous dose levels (A. two subjects at the second (Level 1) dose level or B. two subjects at the third (Level 2) dose level or C. one subject at the second (Level 1) and one at the third (Level 2) dose level). New subjects will be enrolled to the particular dose level (Level 0, 1, or 2) to replace subjects that have not completed the full DLT of nine weeks at the first (Level 0), second (Level 1) or the third (Level 2) dose level. The enrolment of replacing subjects can be conducted without delays. If there is DLT in any subject at any level during the DLT assessment

period, no new subject will be dosed at any dose until the TITE-CRM has been updated. Dosing of the already dosed subjects may continue receiving additional repeated doses if they have not experienced DLT while on repeated dosing and TITE-CRM allows that. Recommendation from the TITE-CRM will be used to guide decisions on the dosing level of the next subject during dose escalation and to guide the MTD decision after completion of Part I. The third and the fourth subject at the highest dose level can be allocated into the trial when two subjects at this level have been observed for the full 9-week DLT period.

4.2.4 DLTs during the DLT Assessment Period after the Dose has been Escalated (Part I)

If the dose levels below the dose that demonstrate unacceptable DLT do not demonstrate DLT, the repeated dosing will be conducted at those dose levels. If an acceptable DLT level has been observed at the repeating dose levels, these levels are right doses for expansion cohorts from the DLT perspective. Immune function, PK and PD data will be used to determine if the dose is suitable for Part II. If none of the tested dose levels (including reserve dose levels -1 and -2 shown in Table 4) demonstrate acceptable safety, the trial will be halted until the Sponsor has amended the protocol or decided to stop the trial.

4.2.5 Delayed Toxicities That Occur after the Full DLT Assessment Period (For Part I subjects and Part II subjects that are in cohorts investigating new exposure levels)

Rules for enrolment halt are applied to all Part I subjects and in Part II to the first six study subjects in a cohort that is exploring a new level of exposure for the first time (i.e. Q2W and Q1W frequencies, and Q3W doses that have not been tested in Part I). This is to ensure the safety of the study subjects during dose exploration in case of potential AEs that occur after the defined DLT period, which could provide a signal to limit the dose. If two DLT evaluable subjects within a particular dose or dosing frequency i.e., in a specific dose escalation cohort have delayed AEs after the DLT assessment period, that would otherwise have been determined as DLTs during the period, enrolment to that cohort and all cohorts that have higher exposure is halted until the DMC has evaluated the cases and made the decision how to proceed. The rule applies only to a specific dose/cohort i.e., one delayed DLT in a cohort testing a certain level of exposure (dose & frequency) is not summed up with another delayed DLT from another dosing scheme. For example, one delayed DLT in 1 mg/kg Q1W and one delayed DLT in 10 mg/kg Q2W do not sum up to two delayed DLTs and contribute to this rule. In case two delayed DLTs occur in the first 6 subjects (DLT evaluable patients) at a particular dose e.g., at 10 mg/kg Q2W, the DMC meeting will be scheduled to evaluate has a maximum tolerated dose been achieved. Delayed DLT occurring beyond the first 6 subjects will be monitored, followed up and presented to the DMC during scheduled meetings. The enrolment halt described above refers to a temporary hold not to dose any new subjects at the dose level that is under DMC evaluation, or any higher dose level. Subjects already receiving the dose, or higher dose, that have not experienced a DLT may continue receiving the drug until DMC resolution or further guidance. Trial activities at lower doses are not affected and can continue as normal. As this enrolment halt is envisaged by the protocol, therefore no substantial amendment informing about the halt will be submitted in these situations. Further actions will be taken according to the DMC recommendation as necessary.

4.3 Dose Escalation to 30, 45 and 100 mg/kg Doses (Q3W, Part II)

Dose level 30 mg/kg and possibly 45 mg/kg and 100 mg/kg are included to investigate further tolerability, safety, receptor occupancy and efficacy in Part II of the study. 3 + 3 design (with additional safety margins/sentinel dosing between first three subjects) will be utilized to investigate these additional dose levels, and if tolerated, dose levels will be expanded to 10 subjects. To ensure safety at high doses the 30 mg/kg Q3W dose level will finish enrolment of all 10 subjects before the

dose can be escalated to 45 mg/kg Q3W. Similarly, the 45 mg/kg Q3W dose level will finish enrolment of all 10 subjects before the dose can be escalated to 100 mg/kg Q3W. These cohorts of ten patients exploring higher doses may consist of subjects with different cancer types of interest. Schedule of assessments in these dose levels is the same as Part II schedule (Table 2). In addition to standard Part II assessments the first three patients undergoing 45mg/kg and 100mg/kg will undergo 24h monitoring in hospital after the first dose.

4.3.1 Enrolment of Subjects (30 - 100 mg/kg Q3W) and Dose Escalation (Part II)

To ensure the safety of the study subjects, the first three subjects at and above the 30 mg/kg dose level will be enrolled stepwise after each has cleared their 28 day DLT observation period. The detailed rules for enrolling the first three subjects on a dose level are described below (4.3.2). If any of the first three subjects dosed at the 30 mg/kg dose level has a DMC verified DLT (see Section 4.1 for DLT definition) within 28 days from the first IMP administration, an additional three subjects will be enrolled on the 30 mg/kg dose level. If a maximum of one of the six subjects experiences a DLT at 30 mg/kg dose level, up to ten subjects will be included in the 30 mg/kg dose level after which the trial can proceed to the next dose level. If at least two of the first three subjects or two of the six subjects experience a DMC verified DLT at the 30 mg/kg dose level, then the MTD has been reached, enrolment to the 30 mg/kg dose level will be placed on hold and dose escalation is terminated. The MTD is defined as the highest dose level, in which the first six subjects were treated with a maximum of one subject experiencing a DLT. Subjects on treatment who have not experienced DLT at that dose level may continue receiving the treatment and the DMC will decide regarding the treatment continuation and possible dose level de-escalation for these particular and DLT experienced subjects. The doses 45 and 100 mg/kg Q3W have the same 3 + 3 dosing rules as described for 30 mg/kg, and if at least two of the first three subjects or two of the six subjects has a DLT, then the MTD has been reached, enrolment to the dose level will be placed on hold, and dose escalation is terminated. If MTD is achieved at the dose level of 30mg/kg Q3W, a reserve de-escalation dose level of 20 mg/kg Q3W may be investigated with the same 3+3 design approach.

4.3.2 Dosing Rules (30 - 100 mg/kg) (Q3W, Part II)

Sentinel dosing will be applied for 30-100mg/kg dosing. The second subject on a particular dose level can receive the first dose only after the first subject has been followed up for 28 days (additional precaution compared to traditional 3+3 model) after the first dose, and has not demonstrated any DLT. The third subject may receive the first dose after the second subject has been followed up for 28 days after the first dose and and neither of the subjects have demonstrated any DLTs. DLT evaluable subject will have at least one dose of IMP and have at least 28 days of follow-up after IMP infusion. If these criteria are not met, the subject will be replaced. Once three evaluable subjects have received at least one dose and have been followed up at for 28 days with no DLTs, all remaining subjects on the dose level may be enrolled without any hold. If any of the first three subjects cannot be followed for the full 28-day DLT observation period for reasons other than DLT, the subject may be replaced in order to obtain the required tolerability information of 28 days from the first IMP infusion, before the remaining subjects on the dose level may be enrolled. The replaced subject will, however, count towards thecohort of 10 subjects. The same rules will apply for the other dose levels.

5 ELIGIBILITY

Subjects registered onto this trial must fulfil all the common inclusion and exclusion criteria and fulfil their disease specific inclusion and exclusion criteria.

5.1 Inclusion and Exclusion Criteria

5.1.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in the clinical trial:

1) Written Informed Consent
2) Aged ≥ 18 years male or female
3) Tumour sample should be collected during screening period. If a recent tumour biopsy obtained within six months before the date of consent is available (or older, as agreed on a case by case basis with the sponsor), that may be used. At the discretion of the sponsor, the tumour sample may be optional for certain subjects in Part III
4) Life expectancy > 12 weeks
5) Histologically confirmed advanced (inoperable or metastatic) malignancies in which (according to the view of the investigator) no curative, effective or suitable treatment options exist.
    - Hepatocellular carcinoma
    - Gallbladder cancer or intra- or extrahepatic cholangiocarcinoma
    - Colorectal adenocarcinoma
    - Serous poorly differentiated (Grade 3) ovarian adenocarcinoma or undifferentiated ovarian cancer
    - Pancreatic ductal adenocarcinoma
    - Immunotherapy (IO) resistant cutaneous melanoma (progression during programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) or CTLA-4 antibody therapy)
    - Uveal melanoma in Parts II and III
    - Gastric adenocarcinoma (including adenocarcinoma of the distal esophagus / GE junction) in Parts II and III
    - ER+ breast cancer in Parts II and III
    - Anaplastic thyroid cancer in Parts II and III
6) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
7) Measurable disease in Parts II and III
8) Adequate bone marrow, liver and kidney function defined as

    Blood white blood cell ≥ lower limit of normal
    Blood neutrophil count ≥ $1x10^9$/L
    Blood platelet count ≥ $100x10^9$/L, for HCC ≥ $50x10^9$/L
    Blood haemoglobin ≥ 9.0 g/dL
    Creatinine clearance > 40 mL/min calculated by Cockcroft-Gault formula
    AST ≤ 3 X ULN (≤ 5 x ULN when HCC or hepatic metastases are present)
    ALT ≤ 3 X ULN (≤ 5 x ULN when HCC or hepatic metastases present)
    Bilirubin ≤ 1.5 X ULN
    Albumin ≥ 3.0 g/dL

    The most recent measurements taken during the screening period must be within the required limits for the patient to be considered eligible (i.e. criteria met once during the screening period are not sufficient if there are more recent measurements available that are not within the required limits. It is however acceptable to repeat measurements if the initial measurements or subsequent measurements taken during the screening period are not within the required limits; the patient is eligible providing that the newest measurements are within the required limits). However, once a subject is out of the screening period, and has had eligibility confirmed and

been enrolled, the pre-dose laboratory assessments are not subjected to inclusion criteria limits, but only for investigators assessment of subject safety.

9) Women of child-bearing potential must have a negative pregnancy test in serum prior to trial entry
10) Women of child-bearing potential and men who have partners of child-bearing potential must be willing to practise highly effective contraception for the duration of the trial and for three months after the completion of treatment

5.1.2 Exclusion Criteria

1) Less than 21 days since the last dose of intravenous anticancer chemotherapy or less than five half-lives from a small molecule targeted therapy or oral anticancer chemotherapy before the first IMP administration
2) Any immunotherapy within preceding 6 weeks from the first IMP administration
3) Investigational therapy or major surgery within 4 weeks before the first IMP administration
4) Active clinically serious infection > Grade 2 NCI-CTCAE version 5.0 (Appendix 5 - Common Toxicity Criteria Gradings) within preceding 2 weeks before the first IMP administration
5) Brain metastases
6) Subject has not recovered from the previous therapies to Grade ≤ 1 severity as classified by the NCI-CTCAE version 5.0 (except Grade ≤ 2 alopecia, neuropathy or thyroid disorders)
7) Pregnant or lactating women
8) History of second malignancy except for non-melanotic skin cancer, cervical carcinoma in situ or superficial bladder cancer, or any other malignancy treated previously with curative intent and more than three years without relapse
9) Evidence of severe or uncontrolled systemic diseases, congestive cardiac failure New York Heart Association (NYHA) class ≥ 2 (Appendix 7 - NYHA classification), Myocardial Infarction (MI) within 6 months or laboratory finding that in the view of the investigator makes it undesirable for the subject to participate in the trial
10) Any medical condition that the Investigator considers significant to compromise the safety of the subject or that impairs the interpretation of IMP toxicity assessment
11) Confirmed human immunodeficiency virus infection
12) Symptomatic cytomegalovirus infection
13) Subjects with active auto-immune disorder (except type I diabetes, celiac disease, hypothyroidism requiring only hormone replacement, vitiligo, psoriasis, or alopecia)
14) The subject requires systemic corticosteroid or other immunosuppressive treatment
15) Subjects with organ transplants
16) Subjects in dialysis
17) Use of Live (attenuated) vaccines for 30 days prior to the start of study treatment, during treatment, and until last visit
18) Subject is unwilling or unable to comply with treatment and trial instructions
19) Subjects with known hypersensitivity to the IMP or any of the pharmaceutical ingredients

5.1.3 Specific Additional Exclusion Criteria for HCC

1) Any ablative therapy (Radio Frequency Ablation or Percutaneous Ethanol Injection) for HCC (this should not exclude subjects if target lesion(s) have not been treated and occurred > 6 weeks prior trial entry)
2) Hepatic encephalopathy
3) Ascites refractory to diuretic therapy
4) Child-Pugh score ≥ 7

6 SCREENING AND CONSENT

6.1 Informed Consent

It is the responsibility of the Investigator to obtain a written informed consent from each subject prior to performing any trial related procedure. A Patient Information and Consent Document is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the subject. The Investigator should also stress that the subject is completely free to refuse to take part or withdraw from the trial at any time. The subject should be given ample time (e.g. 24 hours) to read the Patient Information and Consent Document and to discuss their participation with others outside of the site research team. The subject must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the subject to refuse to participate in the trial without giving a reason must be respected.

If the subject expresses an interest in participating in the trial, they should be asked to sign and date the latest version of the Patient Information and Consent Document. The Investigator must then sign and date the form. A copy of the Patient Information and Consent Document should be given to the subject, a copy should be filed in the hospital notes, and/or in the Investigator Site File (ISF). Once the subject is entered into the trial, the subject's trial number should be entered on the Information and Consent Document maintained in the ISF.

Details of the informed consent discussions should be recorded in the subject's medical notes; this should include the date consent was given and the short name of the trial or protocol code. Throughout the trial, the subject should have the opportunity to ask questions about the trial and any new information that may be relevant to the subjects' continued participation should be shared with them in a timely manner. On occasion, it may be necessary to re-consent the subject, in which case the process above should be followed and the subject's right to withdraw from the trial respected.

Details of all subjects consented onto the trial should be recorded on the Patient Screening and Enrolment Log, and with the subject's prior consent their General Practitioner should also be informed that they are taking part in the trial according to the local requirements. A General Practitioner Letter is provided electronically for this purpose.

6.2 Screening

During the screening period, a subject's eligibility for the trial is determined by evaluation of the exclusion and inclusion criteria. A signed informed consent (see Section 6.1) must be present before starting any screening procedures.

Subjects will undergo a medical history review as part of the screening assessment.

The parameters listed below are collected and recorded into the eCRF during the screening period. Local laboratory parameters are analysed according to standard practice e.g. plasma/serum (the same method should be used throughout the study). All screening procedures must occur within 28 days before the IMP is administered.

- Informed consent
- Demographic data (age, race, and sex)
- Inclusion/Exclusion criteria

- Medical history (current diseases including their treatment history and other relevant medical history)
- Weight
- Concomitant medications, vaccinations and interventional procedures (including herbal products) taken within 28 days prior to the signed consent or during the screening period
- ECOG performance status
- A targeted physical examination covering the major body systems (e.g. general appearance, head [ear, nose and throat], cardiovascular, eyes, respiratory, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin)
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate)
- Electrocardiography (ECG)
- Cytomegalovirus (CMV) infection status (If a subject has no symptoms, the blood test is not needed. However, if an investigator is unsure, then the test should be performed.)
- Blood sampling for
    - Human immunodeficiency virus (HIV) serology
    - Hepatitis B and C virus (immunochemical or nucleic acid test)
    - Complete blood count (CBC: white blood cells, neutrophils, lymphocytes, thrombocytes, haemoglobin)
    - Comprehensive metabolic panel (CMP): (glucose, calcium, sodium, potassium, chloride, creatinine, ALT, alkaline phosphatase (ALP), AST, creatine kinase (CK), total bilirubin, albumin)
    - Endocrine panel: cortisol, lipase, pancreas-specific amylase, thyroid stimulating hormone, parathyroid hormone (PTH), free thyroxine (T4), free triiodothyronine (T3), troponin
- Serum pregnancy test (women of child-bearing potential only)
- Tumour biopsy must be less than 6 months old from the date of consent or taken during the screening period. An archival block, if available, can be used to complement the obtained biopsy. See the Laboratory Manual for sample procurement and handling procedures.
- Brain imaging (computerized tomography (CT)). Routine diagnostic image (CT/ magnetic resonance imaging (MRI)) can be used if available. The brain scan within six weeks prior to the 1st dose is acceptable.
- AE assessment. Photographs to document visible AEs should be considered.

A subject may be re-screened if he/she fails screening but later fulfils the eligibility criteria. If the 28 day screening period has been exceeded, the subject must be re-consented to the trial and a new subject's trial number is created for the subject.

7 TRIAL ENTRY

In Part I, the screening of a subject can only be started when there is an open slot in a cohort, and it has been communicated in writing to which site the available slot has been allocated. Communications regarding the opening of upcoming cohorts and the allocation of slots to sites will be sent to all active investigators/sites to ensure transparency. The trial should not be discussed with a potential subject until a slot has been confirmed for that particular subject. Once a slot or slots has been secured by a particular subject or to the site, the signed informed consent will be obtained (see Section 6.1) and a subject number will be given to the subject(s). The eligibility of each subject will be verified by the Medical Monitor. After the eligibility check and Medical Monitor's enrolment

confirmation, any change in the subject eligibility criteria needs to be reported in the eCRF and the suitability of the subject to enter the study treatment must be carefully evaluated and confirmed by the investigator prior to Cycle 1 dosing. Other hospitals may also refer subjects to the trial, but the screening must occur at the investigative site. During Part I of the trial, confirmation that the TITE-CRM is up to date is required; if DLT information about the assigned subjects is missing from the TITE-CRM, new subjects cannot be dosed until all missing safety data is entered into the system. Once confirmed that the TITE-CRM is up to date, the initial dose of the subject may be determined. If the randomisation is applied during Part I the dose will be provided by system that handles the randomisation. Once assigned, the subject numbers for any screening failures, non-treated, non-evaluable, or discontinued subjects will not be re-used. After Part I has been completed, data has been analysed and the dose has been selected to Part II, TITE-CRM will not be used any more. However, all subjects entering the trial can be administered the IMP only after the Medical Monitor has verified the subject's eligibility.

8 TREATMENT DETAILS

8.1 Investigational Medicinal Product

The IMP is FP-1305 (bexmarilimab). Further details can be found in the latest version of the Pharmacy Manual and Investigator's Brochure.

8.1.1 Dosage Form and Composition

The IMP is clear to opalescent solution intended for intravenous application. Each 10 mL glass vial contains 250 mg of FP-1305 in histidine buffer containing stabilising excipients. The concentration of FP-1305 in the formulation is 25 mg/mL. Each vial is packed into a carton box. Further details of packaging and labelling can be found in the latest version of the Pharmacy Manual.

8.1.2 Instructions for Storage

The IMP must be stored in a secure area according to local regulations at 2-8 °C. Further details can be found in the latest version of the Pharmacy Manual.

8.1.3 Instructions for Handling the Investigational Medicinal Product

The Investigator or other designated trial personnel will maintain a log of all IMP received, dispensed, destroyed, and/or returned. Drug supplies will be inventoried and accounted throughout the trial. Detailed instructions for the handling of the IMP are given in the Pharmacy Manual.

8.2 Trial Treatment

Once the subject has been confirmed to be eligible for the trial by the Simbec-Orion Medical Monitor, the treatment period can start. The Investigator or other designated trial personnel will administer FP-1305 I.V. (peripheral or central venous line) on D1 of each cycle. The infusion rate, duration of infusion, total volume infused, and any interruption in administration will be recorded as source data and will be transferred on the appropriate eCRF page.

8.2.1 First Infusion

- The first FP-1305 infusion should be administered I.V. at an initial rate of 50 mL/h for the first 30 minutes.
- In the absence of a hypersensitivity reaction, the infusion rate may be increased gradually as per the instructions given in the Pharmacy Manual. Infusion rate will be limited based on the dosing level and volume of saline utilised.

- If a hypersensitivity reaction develops, the infusion should be temporarily stopped for up to 3 hours. Upon resolution of the subject's symptoms, the infusion can resume at one-half the rate previously associated with hypersensitivity.
- If the subject's symptoms do not resolve within 3 hours, the administration of FP-1305 should be discontinued for this cycle.
- If a second infusion reaction develops despite a reduced infusion rate, the administration of FP-1305 should be discontinued for this cycle.

All subjects in Part I dose-escalation cohorts must be closely monitored for safety for the first 24 hours after the first IMP infusion at the trial site hospital. Subjects in the dose-expansion cohorts in Part I and in Part II must be monitored for a minimum of 6 hours after the first IMP administration. However, first three subjects testing new doses or dosing frequencies in Part II should be closely monitored for safety for the first 24 h after the first IMP infusion at the trial site hospital. In Part III, all subjects must be monitored for minimum of 4 hours after the first IMP infusion. Any subject who is deemed at risk of tumour lysis syndrome or any other safety concern by the judgement of the treating investigator may be hospitalized for a longer period.

8.2.2 Subsequent Infusions

- Subsequent infusions may be administered at the highest rate that was well tolerated in the preceding cycle, for the first 30 minutes
- In the absence of a hypersensitivity reaction, the infusion rate can be doubled every 30 minutes, to the maximum infusion rate allowed for the dosing level as per instructions given in the Pharmacy Manual
- If a hypersensitivity reaction develops, subjects will be pre-medicated prior to each treatment cycle with:
- Acetaminophen 1000 mg per os 12 h and 30 min prior to the planned infusion time
- Antihistamine (Diphenhydramine 50 mg equivalent) per os 12 h and 30 min prior to the planned infusion time
- Glucocorticoid (Hydrocortisone 100 mg equivalent) I.V. 30 min prior to the planned infusion time
- Variance based on institutional practice is acceptable once discussed with the Sponsor. In addition, the guidelines under First Infusion (Section 8.2) should be followed for the first subsequent infusion.

After the second infusion (Cycle 2), the Part I subjects and in Part II the first three subjects testing new doses or dosing frequencies must be monitored for safety at the clinical facility for a minimum of 6 hours. Other subjects in Part II and subjects in Part III must be monitored for safety for a minimum of 2 hours after the second infusion.
After Cycle 2 the IMP may be administered in the outpatient setting and the subjects must be monitored for safety for a minimum of 2 hours prior to discharge until the end of the treatment. In any part of the trial, post-dose observation will be longer if deemed appropriate.

8.3 Treatment Schedule

The treatment period is divided into cycles. Each cycle in Q3W dosing lasts three weeks (21 days). The IMP will be administered on Day 1 of each cycle (Q3W) for up to one year with the possibility to extend the treatment beyond one year according to routine clinical practice (see Section 8.7.1). If the IMP infusion cannot be administered as scheduled the IMP infusion must be administered as soon as possible. The IMP administration day is counted as Day 1 of the cycle (for delays see Section 8.7).

Protocol Addendum implements more frequent dosings (Q2W and Q1W). Protocol Addendum requires all relevant national approvals in the countries concerned prior to implementation.

8.4 Assessments during Treatment Period

The assessments during the trial are described in the following chapters and also in Table 1 (Part I), Table 2 (Part II) and Table 3 (Part III). Before each IMP administration, a pre-dose physical evaluation is conducted. AEs will be collected during the whole treatment period starting after the signing of the Informed Consent.

8.4.1 Parameters Collected during Pre-Dose Evaluation in Part I

In Part I the pre-dose assessment is done in every cycle for the 1 -year treatment period if not otherwise stated. Pre-Dose assessments maybe taken also up to three days before the Day 1 in each cycle.

- Height (only in Cycle 1)
- Weight
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- A physical examination covering the major body systems (general appearance, head [ear, nose and throat], cardiovascular, eyes, respiratory, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin)
- ECG (in Cycles 1, 2, 4, 6, and every second cycle thereafter; the ECG must be performed also always if clinically indicated)
- ECOG performance status
- Urine dipstick test
- PK sampling (only in Cycles 1, 2, 3, 4 and 5)
- Anti-drug antibody (ADA) sampling (on Cycles 1, 2, 4, 6, and every second cycle thereafter, or if clinically indicated)
- Blood samples
    - CBC
    - CMP
    - Endocrine panel (cortisol, lipase, amylase (pancreas specific) in Cycles 1, 4 and 8; thyroid stimulating hormone, PTH, free thyroxine (T4), free triiodothyronine (T3) on each cycle)
    - Hepatitis B and C virus (quantitative assessment in Cycles 1, 2, 4 and 6 if tested initially positive)
    - LDH
    - LDL
    - AFP (HCC subjects)
    - CRP
    - CA-125 (OC subjects)
    - CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma subjects)
    - CEA (CRC subjects)
- Research blood samples
    - Receptor occupancy and monocytes (RO assay) (only in Cycles 1, 2, 3, and 4)
    - OxLDL (only in Cycles 1, 2, 3, and 4)
    - Flow cytometry (TBNK cells and CD127 FOXP3 Assay) (only in Cycles 1, 2, 3, and 4)
    - Cytokine and chemokine panel (only in Cycles 1, 2, 3, and 4)
    - Blood sample for PBMC isolation (only in Cycles 1 and 4)
- Imaging

  - MRI/CT (The same imaging method (CT, MRI) per subject must be used throughout the trial. The first scan (C1) must be less than 6 weeks old prior the first dose (routine diagnostic image can be used). Cycles 1, 4, 7, 10, and every third cycle thereafter, up to one year. The images have to be taken as close as possible (± 10 days) to the initial schedule even if there are missed IMP doses. If the treatment extends beyond one year, 18- (± 1 month) and 24- (± 1 month) month images from the first dose are mandatory to take if not routinely taken at these timepoints.
- AE assessment; photographs to document visible AEs should be considered
- Concomitant medications and interventional procedures (including herbal products)

8.4.2 Parameters Collected during Pre-Dose Evaluation in Part II

In Part II the pre-dose assessment is done in every cycle for the 1 -year treatment period if not otherwise stated. Pre-Dose assessments maybe taken also up to three days before the Day 1 in each cycle.

- Height (only in Cycle 1)
- Weight
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- A targeted physical examination covering the major body systems (e.g. general appearance, head [ear, nose and throat], cardiovascular, eyes, respiratory, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin)
- ECG (in Cycles 1, 2, 4, 6, and every second cycle thereafter; the ECG must be performed also always if clinically indicated)
- ECOG performance status
- Urine dipstick test
- PK sampling (only in Cycles 1, 2, 3 and 4)
- ADA sampling (on Cycles 1, 2, 4, 6, and every second cycle thereafter, or if clinically indicated)
- Blood samples
  - CBC
  - CMP
  - Endocrine panel (cortisol, lipase, pancreas-specific amylase , thyroid stimulating hormone, PTH, free thyroxine (T4), free triiodothyronine (T3), troponin)
  - Hepatitis B and C virus (quantitative assessment in Cycles 1, 2, 4 and 6 if tested initially positive)
  - LDH
  - LDL Cholesterol
  - AFP (HCC subjects)
  - CRP
  - CA-125 (OC subjects)
  - CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects)
  - CEA (CRC, ER+ BC, gastric adenocarcinoma subjects)
  - CA-15-3 (ER+ BC subjects)
- Research blood samples
  - At selected sites and cohorts only: Blood sample for RO and PBMC isolation (only on Cycles 1 and 2)
  - Blood sample for PBMC isolation when ‘Blood sample for RO and PBMC’ is not collected (only in Cycles 1 and 2)
  - sCLEVER-1 RO sample (Cycles 1, 2 and 3)

  - OxLDL (only in Cycles 1, 2, 3, and 4)
  - Flow cytometry (TBNK cells, CD127 FOXP3 Assay and PD-1 T-Helper Assay) (only in Cycles 1, 2, 3 and 4)
  - Cytokine and chemokine panel (only in Cycles 1, 2, 3 and 4)
  - Circulating tumour deoxyribonucleic acid (ctDNA) requires genetic consent (only in Cycles 1, 2 and 3)
- Serum or urine pregnancy test (women of child-bearing potential only)
- Imaging
  - MRI/CT (The same imaging method (CT, MRI) per subject must be used throughout the trial. The first scan (C1) must be less than 6 weeks old prior the first dose (routine diagnostic image can be used). Cycles 1, 4, 7, 10, and every third cycle thereafter, up to one year. The images have to be taken as close as possible (± 10 days) to the initial schedule even if there are missed IMP doses. If the treatment extends beyond one year, 18- (± 1 month) and 24- (± 1 month) month images from the first dose are mandatory to take if not routinely taken at these timepoints.
- AE assessment; photographs to document visible AEs should be considered
- Concomitant medications and interventional procedures (including herbal products)

8.4.3 Parameters Collected during Pre-Dose Evaluation in Part III

In Part III the pre-dose assessment is done in every cycle for the 1 -year treatment period if not otherwise stated. Pre-Dose assessments maybe taken also up to three days before the Day 1 in each cycle. See also Table 3 and the Laboratory Manual.

- Height (only in Cycle 1)
- Weight
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- A targeted physical examination covering the major body systems (e.g. general appearance, head [ear, nose and throat], cardiovascular, eyes, respiratory, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin)
- ECG (only in Cycle 5; the ECG must be performed also always if clinically indicated)
- ECOG performance status
- PK sampling for population PK
  - For subjects with odd trial numbers (group A) at Cycle 1
  - For subjects with even trial numbers (group B) at Cycle 4
- Subjects with odd trial numbers (group A) only in Cycle 1.
- Subjects with even trial numbers (group B) only in Cycle 4.
- ADA sampling is done only in Cycles 1, 2, 5, 8 and every third cycle thereafter, or if clinically indicated.
- Blood samples
  - CBC
  - CMP
  - Endocrine panel (cortisol, lipase, pancreas-specific amylase , thyroid stimulating hormone, PTH, free thyroxine (T4), free triiodothyronine (T3), troponin)
  - Hepatitis B and C virus (quantitative assessment in Cycles 1, 2, 4 and 6 if tested initially positive)
  - LDH
  - LDL Cholesterol
  - AFP (HCC subjects)

  - CRP
  - CA-125 (OC subjects)
  - CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects)
  - CEA (CRC, ER+ BC, gastric adenocarcinoma subjects)
  - CA-15-3 (ER+ BC subjects)
- Research blood samples
  - OxLDL (only in Cycles 1, 2, 3 and 4)
  - Flow cytometry (TBNK cells, CD127 FOXP3 Assay and PD-1 T-Helper Assay) (only in Cycles 1 and 2)
  - Cytokine and chemokine panel (only in Cycles 1 and 2)
  - Blood sample for PBMC isolation (only in Cycles 1 and 4)
  - ctDNA requires genetic consent (only in Cycles 1, 2 and 3)
- Serum or urine pregnancy test (women of child-bearing potential only)
- Tumour Imaging
  - MRI/CT (The same imaging method (CT, MRI) per subject must be used throughout the trial. The first scan (C1) must be less than 6 weeks old prior the first dose (routine diagnostic image can be used). Cycles 1, 4, 7, 10, and every third cycle thereafter, up to one year. The images have to be taken as close as possible (± 10 days) to the initial schedule even if there are missed IMP doses. If the treatment extends beyond one year, 18- (± 1 month) and 24- (± 1 month) month images from the first dose are mandatory to take if not routinely taken at these timepoints
- AE assessment; photographs to document visible Aes should be considered
- Concomitant medications and interventional procedures (including herbal products)

8.4.4 Samples Collected and Parameters Analysed during and after IMP Administration in Part I

During or after the IMP infusion, parameters for safety and blood samples are collected as follows (see also Table 1 and the Laboratory Manual):

- Vital signs (blood pressure, heart rate, body temperature and respiratory rate)
  - Cycles 1-3: During infusion, 3 additional readings e.g., every 20 minutes for 1 hour. However, the third additional measurement should be performed after the IMP infusion has completed; therefore, if the infusion lasts more than 1 hour, then the third additional measurement may be more than 20 minutes after the second additional measurement. For the subsequent infusions vital signs are to be measured only before and after IMP infusion.
  - in Cycle 1 at 5 hours (+/- 2 hours) after IMP infusion completion
- PK sampling (only in Cycles 1, 2 and 4)
  - 0 h after all IMP has been administered, 1 h (+/- 5 mins), 5 h (+/- 30 mins), D2 (+/- 4 h), D3 (+/- 4 h) D4 (+/- 4 h), D5 (+/- 8 h), and D8 (+/- 24 h) after IMP administration
- Tumour biopsy (only in Cycle 2)
  - Should be obtained within 10 days after the IMP administration. See the Laboratory Manual for sample procurement and handling procedures.
- ECG (only in Cycles 1 and 4)
  - 0 h after the infusion and PK sampling
- Blood samples (only in Cycle 1)
  - CBC on D5 (+/- 4 h)
  - CMP on D5 (+/- 4 h)

- Research blood samples
    - Receptor occupancy and monocytes (RO assay) (only in Cycles 1 and 2) D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h)
    - Flow cytometry (TBNK cells and CD127 FOXP3 Assay) (only in Cycles 1 and 2) D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h)
    - Cytokine and chemokine panel (only in Cycles 1 and 2) D8 (+/-24 h) and D15 (+/- 24 h)
    - Blood sample for PBMC isolation (only in Cycle 1) D5 (+/- 4 h)
- AE assessment. NOTE: AE assessments should be conducted each time the subject is visiting the hospital. Photographs to document visible Aes should be considered.

8.4.5 Samples Collected and Parameters Analysed during and after IMP Administration in Part II

During or after the IMP infusion, parameters for safety and blood samples are collected as follows (see also Table 2 and the Laboratory Manual):

- Vital signs (blood pressure, heart rate, body temperature and respiratory rate)
    - Cycles 1-3: 20 minutes after the start of the infusion, 40 minutes after the start of the infusion and at 1 h after the start of the infusion or at the end of the infusion (immediately after flushing the line), whichever occurs later.For the subsequent infusions vital signs are to be measured only before and after IMP infusion.
    - in Cycle 1 at 5 hours (+/- 2 hours) after IMP infusion completion
- PK sampling (only in Cycles 1 and 2)
    - 0 h after all IMP has been administered, 1 h (+/- 5 mins), 5 h (+/- 30 mins), D2 (+/- 4 h), D3 (+/- 4 h) D4 (+/- 4 h), D5 (+/- 8 h), and D8 (+/- 24 h)
- Tumour biopsy (only in Cycle 2 and if any new lesions)
    - Cycle 2 biopsy should be obtained within 10 days after the IMP administration. See the Laboratory Manual for sample procurement and handling procedures.
    - Biopsy from new lesions is recommended if assessed feasible by the investigator considering the location of the lesions and condition of the subject.
- ECG (only in Cycles 1 and 4)
    - 0 h after the infusion and PK sampling
- Blood samples
    - CBC on D5 (+/- 8 h) (only in Cycle 1)
    - CMP on D5 (+/- 8 h) (only in Cycle 1)
    - CMP on D8 (+/- 24h) (only in Cycles 2 and 3)
- Research blood samples
    - At selected sites and cohorts only: Blood sample for RO and PBMC isolation (only in Cycle 1) D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h)
    - Blood sample for PBMC isolation when ‘Blood sample for RO and PBMC’ is not collected (only in Cycle 1) D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h)
    - sCLEVER-1 RO sample (only in Cycles 1 and 2) D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h)
    - Flow cytometry (TBNK cells, CD127 FOXP3 Assay and PD-1 T-Helper Assay) (only on Cycles 1 and 2) D2 (+/- 4 h), D8 (+/- 24 h) and D15 (+/- 24 h)
    - Cytokine and chemokine panel (only on Cycles 1 and 2) D8 (+/-24 h) and D15 (+/- 24 h)
- AE assessment. NOTE: AE assessments should be conducted each time the subject is visiting the hospital. Photographs to document visible AEs should be considered.

8.4.6 Samples Collected and Parameters Analysed during and after IMP Administration in Part III

- During or after the IMP infusion, parameters and blood samples are collected as follows (see also Table 3):
- Vital signs (blood pressure, heart rate, body temperature and respiratory rate)
    - Cycles 1-3: 20 minutes after the start of the infusion, 40 minutes after the start of the infusion and at 1 h after the start of the infusion or at the end of the infusion (immediately after flushing the line), whichever occurs later.For the subsequent infusions vital signs are to be measured only before and after IMP infusion.
- PK sampling for population PK
    - For subjects with odd trial numbers (group A) PK sampling will be at Cycle 1 Day 2 (+/- 2 h), at Cycle 1 Day 5 (+/- 24 h), at Cycle 2 Day 1 four hours (+/- 2 h) after all IMP has been administered, and at Cycle 4 D3 (+/- 24 h)
    - For subjects with even trial numbers (group B) PK sampling will be at Cycle 1 Day 1 four hours (+/-2 h) after all IMP has been administred, at Cycle 1 Day 3 (+/- 24 h), at Cycle 2 Day 2 (+/- 2 h), and at Cycle 4 Day 5 (+/- 24 h)
- Tumour biopsy (only in Cycle 2 and if any new lesions)
    - Cycle 2 biopsy should be obtained within 10 days after the IMP administration. See the Laboratory Manual for sample procurement and handling procedures.
    - Biopsy from new lesions is recommended if assessed feasible by the investigator considering the location of the lesions and condition of the subject.
- Blood samples
    - CMP on D5 (+/- 8 h) (only in Cycle 1)
    - CMP on D8 (+/- 24h) (only in Cycles 2 and 3)
- Research blood samples (Cycle 1 only)
    - Flow cytometry (TBNK cells, CD127 FOXP3 Assay and PD-1 T-Helper Assay) on D8 (+/- 24 h) and D15 (+/- 24 h)
    - Cytokine and chemokine panel on D8 (+/- 24 h) and D15 (+/- 24 h)
    - Blood sample for PBMC isolation on D8 (+/- 24 h)
- AE assessment. NOTE: AE assessments should be conducted each time the subject is visiting the hospital. Photographs to document visible AEs should be considered.

8.4.7 Tumour Assessment

Tumour assessment is done at the treating site according to RECIST 1.1 (Eisenhauer et al. 2009; Appendix 1 - RECIST Criteria) and Immune-related response criteria (Appendix 2 - Immune-related Response Criteria). MRI/CT (chest, abdomen and pelvis) slice thickness must be 5 mm or less. In case of suspicion of pseudoprogression and subjective stable disease (no clinical deterioration) a second tumour evaluation should be carried out at least 4 weeks after the first response evaluation even if the subject has been deemed to discontinue from the study. For evaluable subjects, the response will be reported in each cohort as the numbers of subjects who have CR, PR, SD, or progressive disease as well as irCR, irPR, irSD, or ir-progressive disease.

8.5 Assessments during the Post-Treatment Period

The post-treatment period starts once the subject has completed the treatment period or stopped the treatment permanently (see Section 10.4). Once it has been decided that a subject will permanently stop treatment, a Follow-up Visit should be performed 4 weeks (+/- 1 week) after their last dose of IMP. If the last IMP dose was >5 weeks at the time of the decision, the Follow-up Visit should be performed as soon as possible. If the subject discontinued the treatment period due to AEs, the subject

must be followed up until the AEs have resolved or no change is the AE status is observed over the period.

- Vital signs (blood pressure, heart rate, body temperature and respiratory rate).
- A targeted physical examination covering the major body systems (e.g. general appearance, head [ear, nose and throat], cardiovascular, eyes, respiratory, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin)
- ECG (in Part I and II)
- ECOG performance status
- ADA sampling
- Blood samples
    - CBC
    - CMP
    - LDH
    - LDL Cholesterol
    - AFP (HCC subjects)
    - CRP
    - CA-125 (OC subjects)
    - CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects)
    - CEA (CRC, ER+ BC, gastric adenocarcinoma subjects)
    - CA-15-3 (ER+ BC subjects)
- Serum pregnancy test (women of child-bearing potential only)
- AE assessment. Photographs to document visible AEs should be considered.
- Concomitant medications and interventional procedures (including herbal products)

8.6 Sample Collection

8.6.1 Tumour Paraffin Blocks

Tumour biopsy samples will be collected according to the schedule shown in Table 1, Table 2 or Table 3, and following the instructions in the Central Laboratory Services Manual. As indicated, tumour biopsy may be collected also if any new lesions are present. Biopsy from new lesions is recommended only if assessed feasible by the investigator considering the location of the lesions and condition of the subject. Tumour paraffin blocks or cut slides thereof with a notification that the sample contains tumour cells will be sent to the central laboratory for CLEVER-1 assessment by e.g. immunohistochemistry. Other biomarkers and gene expression may be analysed and genetic analysis may be conducted with appropriate methods.
The blocks collected prior to consent will be returned to the study site on request and latest after the trial has ended. The genetic analyses are optional for all subjects entering the trial and will involve a separate subject consent procedure. Consenting to genetic sampling is not a prerequisite to participating in the main trial. Tumour samples collected due other reasons (e.g. unscheduled biopsy or another informative sample for clinical reasons) may be analysed for scientific purpose when available.

8.6.2 Blood Samples

Blood samples will be collected at defined time points (see Table 1, Table 2 and Table 3 as well as the Central Laboratory Services Manual) and for additional research and development related to FP-1305, cancer treatment and disease pathology. PBMCs will be isolated from the blood samples. These cells may also be used for the extraction of ribonucleic acid (RNA)/DNA i.e, genetic analyses may

be conducted from these samples. The genetic analyses are optional for all subjects entering the trial and will involve a separate subject consent procedure. The subjects that give genetic consent will also have blood collected for ctDNA samples and subsequent analysis. Consenting to genetic sampling is not a prerequisite to participating in the main trial. RNA/DNA samples will be destroyed at latest 10 years after completion of this trial. If the subject withdraws the consent, the sample will be destroyed without undue delay. The samples will be sent to the central laboratory and will be analysed in Europe and the US. Specific details about blood sample collection, preparation and storages are provided in the Laboratory Manual. In addition, blood samples will be collected for local analyses e.g. for safety monitoring purposes. Auto-antibodies against liver can be considered in immune-related AEs.

8.7 Dose Modifications, Infusion Delays, Missed Doses and Special Cases

IMP infusion will be prepared based on the subject's predose weight at each cycle (if not available, the most recent weight should be used). No visit specific dose adjustments are allowed for FP-1305, except for weight change adjustments. However, the maximum amount of FP-1305 in one IMP infusion is 10 g and cannot be exceeded irrespective of the weight-based dose. Guidance will be provided in the Pharmacy Manual to ensure calculated doses do not exceed this limit. If the IMP cannot be administered at the scheduled visit for any reason, the IMP must be administered as soon as possible, below here are instructions for Q3W schema. Instructions for Q2W and Q1W schemas are in Protocol Addendum.

- If the delay is 1 to 7 days, the procedures based on the current visit should be performed, and the subsequent visit will follow 21 days from the date of the infusion that occurred.
- If the delay is more than 7 days, the dose is considered missed, and the next per protocol visit should be brought forward and performed as soon as possible. Note, that the tumour images are still to be taken at every scheduled time point
    - (e.g. if there is an eight day delay for Cycle 4 Day 1, Cycle 4 IMP is considered a missed dose. The infusion given eight days after the original schedule in this case is Cycle 5 IMP dose and the related Cycle 5 procedures should be performed. In addition, tumour imaging of Cycle 4 should be done.) The subsequent visit will follow 21 days from the date of the infusion that just occurred.
    - Cycle 2 is an exception: every effort should be made to ensure that Cycle 2 is not delayed. In unavoidable delay, Cycle 2 IMP administration and the related Cycle 2 procedures should be performed as soon as possible.

Subjects that miss two consecutive scheduled doses (more than 49 days from the previous dose) will discontinue the treatment and enter the follow-up period unless specific consultation and agreement occurs between the investigator, the Medical Monitor and the Sponsor justify continued trial therapy. These decisions must be carefully documented.

Additionally, intra-subject dose change may occur to the recommended Part II/Part III dose after it has been determined. This decision must be carefully documented.

8.7.1 Treatment beyond One Year

In case that, as judged by the investigator, it would be beneficial to continue the treatment beyond one year, the protocol allows the treatment according to normal clinical practice, in order to allow the treatment continuation of the study subjects, provided that the clinical development and manufacturing of FP-1305 continues and it is not available via other routes. If the treatment is continued beyond one year, the following procedures/assessments will be done:

- FP-1305 infusion every three weeks
- Collection of weight, vital signs, physical examinations, ECOG, CBC, and CMP pre-dose for every infusion during the second year of treatment
- All available clinical routine images will be utilized. 18- (± 1 month) and 24- (± 1 month) month images from the first dose are mandatory to take if not routinely taken at these timepoints
- Collection of treatment related adverse events
- Collection of survival data (limited to 1 year from the last IMP dose if the treatment has been continued beyond one year)

8.7.2 Treatment Hold in Complete Response

If a study subject meets the irRECIST criteria for a confirmed complete response, the treatment can be placed on hold. The subject should complete follow-up visit but continues in the trial without treatment (FP-1305). Surveillance is conducted using routine good medical care and the results with AE evaluation will be reported to the Sponsor. The treatment with FP-1305 can be continued if the disease progresses (Trial duration and Treatment extension beyond one year definitions shall apply) and the trial is still ongoing. The decision of re-initiation must be agreed between the investigator, the Medical Monitor and the Sponsor and carefully documented to justify the decision. A written informed consent for treatment re-initiation will be obtained before the treatment can be started. The subject will enter to the study using the same subject number as before discontinuation. Relevant medical data received post study completion/ discontinuation will be collected in the eCRF once the subject has given the written consent for the re-initiation. The following pre-dose assessments will be performed prior to the re-initiation:

- CT/MRI scan
- ADA
- Vital signs, physical examinations, ECOG, CBC, and CMP

Once the treatment has been reinitiated, 'Treatment Beyond One Year' procedures will apply to each cycle. Tumour imaging will be performed at 2, 4, 6, 9, 12, 18 and 24 months timepoints after re-initiation of the treatment and ADA will be collected at the end of the treatment and if clinically indicated. The subject will receive the dose used in the study at the time of the re-initiation, even if the subject was previously on another dose. Once it has been decided that a subject will permanently stop treatment, a Follow-up Visit should be performed 4 weeks (+/- 1 week) after their last dose of IMP. If the last IMP dose was >5 weeks at the time of the decision, the Follow-up Visit should be performed as soon as possible.

8.8 Possible Toxicities

There is no experience about using FP-1305 in humans. Thus, the possible toxicities are based on the mode of action (MoA) of the drug and other drugs in this class as well as on a nonclinical toxicity study conducted in monkeys. The following toxicities can be possible:

Infusion reactions: These typically develop within 30 minutes to two hours after the initiation of the drug infusion, although symptoms (headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia) may be delayed for up to 24 hours. Most reactions occur after the first or the second exposure to the agent, but between 10 and 30 percent occur during the subsequent treatments. In general, the likelihood of an infusion reaction declines with each subsequent course of therapy. Proper management should take place in case these types of reactions occur (see Section 8.9.1 for general advice for treatment).

Cytokine release syndrome/Cytokine storm: The cytokine-release syndrome resembles type 1 hypersensitivity reaction and may be clinically indistinguishable. The symptoms are generally mild to moderate in severity and usually occur within the first couple of hours after starting the infusion, predominantly with the first infusion. Based on the antibody properties (no complement binding activation, no Fc-gamma receptor binding) and the lack of increased cytokine release in cytokine release assay *in vitro*, rapid onset cytokine storm is not expected (see Section 8.2.1 and Section 8.9.1 for general advice for treatment).

Immune-related adverse events: These are dependent on the MoA properties of the used drugs. Whenever agents that potentiate the immune system activation are used, there is a possibility that the immune system also attacks the healthy tissues. The onset of these events depends on the agents used, but the most widely experience is obtained from the immune checkpoint inhibitors (CTLA-4 or PD-[L] 1 targeting agents). The symptoms typically develop relatively late (weeks to months) during the course of the agent administration. Usually they are mild to moderate in intensity. With PD-1 therapy, the incidence of severe (Grade 3 to 4) events is low. They most commonly involve the skin, the GI tract, and the endocrine organs.

Based on the MoA properties, FP-1305 is predicted to induce immune cell activation. This activation might lead to immune-related adverse reactions. Thus, special attention should be given to fever, diarrhoea, colitis, transaminase or total bilirubin elevations, signs and symptoms of nephritis, renal dysfunction, endocrinopathies, hyperglycaemia, changes in the thyroid function, or rash. Study subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble symptoms caused by e.g. brain metastasis or the underlying disease. However, since FP-1305 is suspected to only induce direct tumour effects, the likelihood of irAEs is expected to be low.

Tumour lysis syndrome: Tumour lysis syndrome is an oncologic emergency that develops most often in patients with non-Hodgkin's lymphoma or acute leukaemia, its frequency is increasing among patients who have tumours that used to be only rarely associated with this complication. The onset may vary, but after Rituximab (EU)/Rituxan (US) therapy it occurs after 12-24 hours of the first infusion. It occurs when tumour cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalaemia, hyperphosphatemia, and hypocalcaemia. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death due to multiorgan failure. Hyperphosphatemia with calcium phosphate deposition and/or the precipitation of uric acid in the renal tubules can also cause acute kidney injury.

With the emergence of new effective and targeted anticancer drugs or new combinations of drugs, tumour lysis syndrome has also been observed in patients with cancers that were previously rarely associated with this complication. At least one case of tumour lysis syndrome has been observed with anti-CSF1R therapy. It is possible that also FP-1305 can cause tumour lysis syndrome because it can direct cytotoxic T-cells to kill tumour cells. FP-1305 may also impair macrophage phagocytosis function, a MoA that may predispose to tumour lysis syndrome if a massive anti-tumour effect is achieved.

Increased fibrosis in response to liver injury: Fibrosis of the liver is an excessive accumulation of scar tissue that results from ongoing inflammation and liver cell death that occurs in most types of chronic liver diseases. Nodules, abnormal spherical areas of cells, form as dying liver cells are replaced by regenerating cells. This regeneration of cells causes the liver to become hard. Fibrosis

refers to the accumulation of tough, fibrous scar tissue in the liver. Preclinical models have demonstrated that CLEVER-1 expressing endothelial cells and macrophages may remove products of oxidative stress, thereby preventing low-level continuous injury and scarring. Since FP-1305 most likely impairs this function it is possible that the risk of fibrosis of the liver may increase if a patient has a condition that induces liver injury.

8.9 Management of Toxicities

All AEs should be graded according to Section 11.3.1 and proper action taken based on the clinical findings and grading.

In the following, when a limit for a laboratory parameter in plasma is indicated and the local practice is to have the test in serum, the equivalent value should be considered, and vice versa.

FP-1305 should be withheld for any of the following adverse event at least possibly related to FP-1305:

1) Grade 2 pneumonitis (see Section 8.9.2.1)
2) Grade 2 or 3 colitis (see Section 8.9.2.2)
3) Grade 2 nephritis (see Section 8.9.2.3)
4) Grade 2 liver enzyme elevations (see Section 8.9.2.4)
5) Grade 2 or 3 endocrinopathy (see Section 8.9.2.5)
6) Grade 2 fibrosis due to liver injury (see Section 8.9.4)
7) Any other severe or Grade 3 treatment-related adverse reaction
8) Prolonged (> 2 weeks) Grade 2 or intolerable Grade 2 toxicity

FP-1305 must be permanently discontinued for any of the following adverse event at least possibly related to FP-1305:

1) Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy and/or immunosupressants)
2) Grade 3 or 4 infusion reaction (see Section 8.9.1)
3) Grade 3 or 4 pneumonitis or Grade 2 recurring pneumonitis (see treatment in Section 8.9.2.1)
4) Grade 4 colitis (see Section 8.9.2.2)
5) Grade 3 or 4 nephritis (see Section 8.9.2.3)
6) Grade 3 or 4 hepatitic failure (see Section 8.9.2.4)
7) Grade 4 endocrinopathy (see Section 8.9.2.5)
8) Grade 3 or 4 fibrosis due to liver injury (see Section 8.9.4)
9) Inability to reduce the corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 6 weeks from the initiation of the continuous corticosteroid
10) Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy and/or immunosupressants) that do not recover to Grade 0-1 within 6 weeks after the last dosing of FP-1305 and that are considered clinically significant
11) Any haematological or non-haematological Grade 3 treatment-related adverse reaction that recurs

8.9.1 Infusion Reactions

In case of an infusion reaction, the following documentation should be recorded

1) Pre-infusion assessment (i.e., the drugs administered, doses, number of previous infusions of the agent, and infusion rates)
2) Initial symptoms and course of progression

3) Time when the infusion was initiated and time when the infusion reaction began
4) Intervention, timing, and subject response
5) Time of symptom resolution

Infusion reactions are generally not considered to be DLT, but this judgement should be conducted after each case. Severe (Grade 3 or 4) reactions should be reported within 24 hours to the Sponsor.

Grade 1 infusion reaction (Mild reaction; no infusion interruption or intervention necessary)
Monitor the subject closely or treatment according to the local practise. Consider prophylactic medication (e.g., paracetamol a.k.a. acetaminophen and diphenhydramine) for next administration.

Grade 2 infusion reaction (Moderate reaction leading to infusion interruption but responsive to symptomatic treatment): Interrupt the infusion but maintain vascular access with normal saline. Paracetamol (a.k.a. acetaminophen) and diphenhydramine (or other antihistamine according to local practises) usage is recommended or treatment according to the local practise. However, diphenhydramine (50 mg) and ranitidine (50 mg diluted in 5% dextrose to 20 mL) given together for anaphylaxis are superior to diphenhydramine given alone. Vital sign assessment should be periodically repeated until the subject is stable. Once the symptoms are totally resolved, the infusion may be restarted at maximum 50% of the previous infusion rate. If the symptoms do not recur during 30 minutes of infusion of this slower rate, the infusion rate may be increased to the normal rate. If symptoms recur, the infusion must be stopped, and the amount infused should be reported. Prophylactic medication for the next administration is highly recommended and the infusion rate should be adjusted (see Section 8.2.1 and Section 8.2.2).

Grade 3 or 4 infusion reaction (A prolonged reaction that does not rapidly respond to symptomatic treatment, with possible recurrence of symptoms following initial improvement, hospitalization indicated for the clinical sequelae, or life-threatening requiring pressor or ventilatory support): Interrupt the infusion but maintain a vascular access with normal saline. Epinephrine should be considered depending on the severity of the reaction. Corticosteroids may be given IV or orally; oral administration is sufficient in less severe anaphylactic events. Vital sign assessment should be periodically repeated until the subject is stable. The administration of FP-1305 is permanently discontinued.

8.9.2 Immune Related Adverse Events

The aetiology of symptoms that may suggest an irAEs should always be investigated in order to rule out symptoms due to infection or disease progression. Systemic use of corticosteroids is generally prohibited (see Section 10.2) because a decrease in immune cells in circulation is observed after initiation of corticosteroid treatment and it may counteract the effect of the IMP. Thus, it needs to be carefully evaluated, if the continuation in the study is beneficial for the subject. In such cases, investigator should consult the Sponsor and Medical Monitor for subject continuation.

8.9.2.1 Immune-Mediated Pneumonitis

Monitor subjects for signs and symptoms of pneumonitis. A CT should be performed to confirm diagnosis. Corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Permanently discontinue FP-1305 for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold FP-1305 until the resolution for moderate (Grade 2) pneumonitis. If Grade 2 pneumonitis recurs FP-1305 must be permanently discontinued.

8.9.2.2 Immune-Mediated Colitis

Monitor subjects for immune-mediated colitis. Subjects with Grade 3 or Grade 4 diarrhoea as well as those with Grade 2 diarrhoea with blood in the stools should be evaluated for the presence of colitis. Diagnosis with endoscopy should be considered. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Withhold FP-1305 for Grade 2 or 3 immune-mediated colitis. Permanently discontinue FP-1305 for Grade 4 colitis or for recurrent colitis upon restarting the drug.

Consider adding an agent or other immunosuppressant agents, such as an anti-TNF antibody therapy, for the management of immune-mediated colitis unresponsive to systemic corticosteroids within 3 to 5 days or recurring after symptom improvement. If other immunosuppressive agents are needed for the management of immune-mediated colitis, FP-1305 should be permanently discontinued.

8.9.2.3 Immune-Mediated Nephritis and/or Renal Dysfunction

Corticosteroids should be used (initial dose of 1 to 2 mg/kg/day prednisone or equivalent) for Grade 2 or greater nephritis (creatinine 2 - 3 x above baseline). Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Withhold FP-1305 for moderate (Grade 2) nephritis, and permanently discontinue FP-1305 for severe (Grade 3) or life-threatening (Grade 4) nephritis.

8.9.2.4 Immune-Mediated Hepatitis and/or Liver Dysfunction

Liver tests should be periodically performed (according to the schedule). If immune-mediated hepatitis is suspected, corticosteroids should be used (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater transaminase elevations (Grade 2 transferase levels >3.0 - 5.0 x ULN if baseline value was normal; >3.0 - 5.0 x baseline if baseline value was abnormal) or bilirubin elevations (Grade 2 >1.5 – 3.0 x ULN if baseline value was normal; >1.5 – 3.0 x baseline if baseline value was abnormal).

Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. In steroid refractory subjects, the use of mycophenolate mofetil 500-1000mg twice a day may be considered and FP-1305 should be permanently discontinued. A liver biopsy should be considered to confirm the diagnosis.

In case of suspected immune-mediated hepatitis related to FP-1305 withhold FP-1305 for moderate (Grade 2) liver enzyme elevation, and permanently discontinue FP-1305 for severe (Grade 3) or life-threatening (Grade 4) hepatic failure if the increase is not clearly related to cancer progression in the liver.

8.9.2.5 Immune-Mediated Endocrinopathies

Subjects should be monitored for clinical signs and symptoms of endocrinopathies. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or

underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

Withhold FP-1305 for symptomatic hypothyroidism and initiate thyroid hormone replacement if needed. Withhold FP-1305 for symptomatic hyperthyroidism and initiate antithyroid medication if needed. If an acute inflammation of the thyroid is suspected, corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone equivalents) should be considered. Upon improvement, administration of FP-1305 can be resumed after corticosteroid taper. FP-1305 must be permanently discontinued for life-threatening (Grade 4) hyperthyroidism or hypothyroidism. Monitoring of thyroid function should be continued to ensure appropriate hormone replacement is utilised.

Withhold FP-1305 for symptomatic Grade 2 adrenal insufficiency and initiate physiologic corticosteroid replacement if needed. FP-1305 must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should be continued to ensure that appropriate corticosteroid replacement is utilised.

Withhold FP-1305 for symptomatic Grade 2 or 3 hypophysitis, and initiate hormone replacement as needed. If an acute inflammation of the pituitary gland is suspected, corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent) should be considered. Upon improvement, administration of FP-1305 can be resumed after corticosteroid taper. FP-1305 must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should be continued to ensure appropriate hormone replacement is utilised.

Withhold FP-1305 for symptomatic diabetes, and initiate insulin replacement as needed. FP-1305 must be permanently discontinued for life-threatening (Grade 4) diabetes. Monitoring of blood sugar should be continued to ensure appropriate insulin replacement is utilised.

Adequate evaluation should be performed to confirm aetiology of symptoms related to irAEs. Consultation of endocrinologist is recommended when endocrinopathy is suspected.

8.9.3 Tumour Lysis Syndrome

Tumour lysis syndrome is generally not considered to be DLT. The syndrome should be reported in 24 hours to Sponsor if Grade 3 or Grade 4.

When there is a suspicion of a tumour lysis syndrome (plasma phosphate level >4.5 mg/dL (1.5 millimole per litre (mmol/L), plasma potassium level >6.0 mmol/L, and plasma albumin corrected calcium <7.0 mg/dL (1.75 mmol/L) or ionized calcium <1.12 (0.3 mmol/L), treatment with intravenous fluids and phosphate binders should be initiated. Rasburicase, a recombinant urate oxidase enzyme, should be considered if serum creatinine levels increase 2.0–2.9 fold from the baseline. If the increase is higher, rasburicase treatment should be started immediately. When subjects are treated with rasburicase, the blood samples used for the measurement of the uric acid level must be placed on ice to prevent ex vivo breakdown of the uric acid by rasburicase and thus obtaining a spuriously low level.

The administration of FP-1305 can be continued when a tumour lysis syndrome occurs, especially when cancer is responding to the treatment. However, prophylactic medication (allopurinol 300 to 800 mg/day in divided doses) may be considered, and proper intravenous hydration should be ensured.

8.9.4 Increased Fibrosis in Response to Liver Injury

Subjects should be continuously monitored with laboratory analyses and physical assessment to ensure adequate liver function. FP-1305 should be withheld when Grade 2 (NCI-CTCAE version 5.0) AST, ALT or total bilirubin elevation is detected, and there is no evidence for cancer progression in the liver or other IMP non-related medical cause that might explain the increase. The IMP administration can be reinitiated when the liver enzyme values decrease to Grade <2 after discontinuation of FP-1305. If the adverse reaction recurs, indicating causal relationship to FP-1305, it must be permanently discontinued.

FP-1305 must be permanently discontinued if Grade 3-4 (NCI-CTCAE version 5.0) AST, ALT or total bilirubin elevation is detected in the absence of cancer progression in the liver or other IMP non-related medical cause that might explain the increase. For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, FP-1305 must be permanently discontinued when AST or ALT increases by ≥3 times from the baseline and lasts for at least 1 week in the absence of cancer progression or other IMP non-related medical cause that might explain the increase.

Proper diagnosis of the liver injury is encouraged.

8.10 Treatment beyond RECIST defined disease progression

In case of suspicion of pseudoprogression and subjective stable disease (no clinical deterioration), a second tumour evaluation should be carried out at least 4 weeks after the first response evaluation even if the subject has been deemed to discontinue from the study.
Subjects treated with FP-1305 may continue treatment beyond initial RECIST 1.1 defined progressive disease, assessed by the investigator, as long as they meet the following criteria (assessment of the criteria must be recorded in the source data):

1) Investigator-assessed clinical benefit
2) Tolerance of study treatment
3) Stable or improved ECOG performance status
4) Treatment beyond progression will not delay an imminent intervention to prevent seriouscomplications of disease progression (e.g., central nervous system (CNS) metastases)

A follow-up scan should be performed after 4 weeks to determine whether there has been a decrease in the tumour size or continued progressive disease. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with FP-1305. If the investigator feels that the subject continues to receive clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring. For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumour burden with a minimum 5 mm absolute increase from the time of the initial progressive disease. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the time of initial progressive disease. FP-1305 treatment should be discontinued permanently upon documentation of further progression.

8.11 Treatment Compliance

The Investigator and the trial personnel should ensure that each subject receives the right dose of FP-1305 as scheduled.

9 SUPPORTIVE TREATMENT

See Section 10.1 and Section 10.2 for allowed and prohibited interventions, respectively.

10 CONCOMITANT INTERVENTIONS / MEDICATIONS

10.1 Allowed Interventions

The subject's regular medication for other diseases
Palliative radiotherapy to bone metastases and non-target lesions on RECIST
Scheduled biopsies of the tumour
Corticosteroids with minimal absorption (topical, inhaled or intranasal) may be used if on a stable dose
All other interventions/medications/vaccines not listed in the prohibited interventions

10.2 Prohibited Interventions

Continuous use of immunosuppressive drugs
Systemic chemotherapy
Systemic corticosteroids other than replacement therapy (primary or secondary adrenal insufficiency) or used for treatment for infusion reaction,or as instructed in this protocol
Other investigational agents
Radiotherapy to the primary tumour or target lesions
Major surgery unless vital indication
Live (attenuated) vaccines

Medication that is necessary for the subject must not be stopped. Otherwise, prohibited interventions must be stopped prior to treatment with FP-1305 as defined in the exclusion criteria (Section 5.1); or at least five half-lives prior to treatment with FP-1305 if no definition is given in Section 5.1.

If a subject requires treatment with systemic corticosteroids (oral or I.V.) after treatment with FP-1305 has been started this must be discussed and approved in advance (in written) by the Medical Monitor or the Sponsor (except for FP-1305 treatment related adverse effects as indicated in this protocol and emergency cases e.g. spinal cord compression and progressing brain metastases in which steroids are needed immediately as assessed by the Investigator).

10.3 Contraception and Pregnancy

Women of childbearing potential (i.e. not post-menopausal or surgically sterilised) must use highly effective methods of contraception (e.g. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; progestogen-only hormonal contraception associated with inhibition of ovulation; intra-uterine device (IUD); intrauterine hormone-releasing system (IUS) or vasectomised partner) to prevent pregnancy or abstain* from heterosexual activity for the duration of the trial and for at least 3 months following treatment discontinuation. In addition, barrier contraception (with or without spermicide) may be used but this should not be considered as an adequate form of contraception on its own.
*Abstinence must be in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

Fertile men whose partners could be of childbearing potential should routinely use a condom during the study and for 3 months thereafter. The partner, if not pregnant, should also use a reliable form of contraception such as the oral contraceptive pill or an IUD.

Refer to Section 11.4.1 if a pregnancy is reported, either that of a female participant, or the partner of a male participant.

Female participants should not breast feed during the treatment period and for at least 3 months after the last infusion of the IMP.

10.4 Trial Subject Withdrawal/Discontinuation

Administration of the IMP and the subject´s participation in the study must be discontinued for any of the following reasons:

1) Withdrawal of informed consent
2) In the case of any clinical AE, laboratory abnormality or illness leading to the conclusion by the investigator that participation into the trial is not the best interest of the subject
3) In the occurrence of toxicities as defined in Section 8.9
4) Pregnancy
5) Termination of the trial by the Sponsor
6) Loss of ability to freely provide informed consent
7) Inability to comply with protocol
8) Disease progression (for treatment beyond RECIST defined disease progression see Section 8.10)
9) Dosing delays greater than the maximum allowed dosing delays as defined in Section 8.7

All trial subjects should comply with the protocol specified follow-up procedures as outlined in Section 8.5. The only exception to this requirement is a withdrawal of informed consent for all trial procedures or when a subject has lost the ability to consent freely. All data collected until the withdrawal of informed consent will be analysed and included into trial data.

10.5 COVID-19 Vaccination

The outcome of the risk assessment conducted by Faron and the study team is that a COVID-19 vaccine given to a trial subject is considered as a simple concomitant medication with no interaction that requires advice on timing of the vaccine or any other aspect.

Treatment with FP-1305 during an ongoing round of vaccination will not, as far as Faron and the study team are aware of, compromise the efficacy of any COVID-19 vaccines. The study team will continue to review and monitor any update in terms of COVID-19 vaccine interaction with molecules targeting macrophages.

Investigators should follow the study protocol, local prescribing guidance and policies when considering if vaccination against COVID-19 is appropriate for subjects participating in this study.

11 ADVERSE EVENT REPORTING

11.1 Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with International Conference on Harmonisation (ICH) GCP, European Union, and national regulations and requirements. The definitions of different types of AE are listed in Appendix 4 - Definition of Adverse Events25.

In summary, the AE collection should comply with the following principles:

1) care should be exercised to collect AEs
2) follow-up period of 4 weeks (+/- 1 week; until follow-up visit) after the last dose does not have exceptions for AE collection. In circumstances where follow-up visit will not be performed, the follow-up period for AE reporting is 4 weeks from last dose of IMP.
3) if the study subject discontinues from the study, also collection of new AEs is discontinued at the follow-up visit, with the exception of follow-up for the IMP-related AEs (see Section 11.6). Survival information should be collected at 1 year and 2 years after the first IMP dose directly from the subject/caregiver or hospital records, or at 1 year after the last IMP dose if the treatment has been continued beyond one year
4) survival data collection after the last dose is not subjected for active AE collection
5) if an investigator becomes aware of a Serious Adverse Drug Reaction after the subject's discontinuation, or during the survival data collection period after treatment, this event should be reported immediately per the standard SAE reporting practices (see Section 11.4)

11.2 Definition of Adverse Event

An AE is any untoward medical occurrence in a study subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

11.3 Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by observation, by spontaneous unsolicited reports of subjects, and, where appropriate, by routine open questioning.

As this is a first in human trial, all medical occurrences which meet the definition of an AE (Section 5)) should be recorded. Disease progression will be recorded as an AE/SAE in this study.

Any **pre-existing conditions** or abnormal laboratory findings present at screening should be recorded in the medical history and should not be recorded as an AE unless the condition worsens by at least one CTC grade during the trial.

Abnormal laboratory findings (e.g., biochemistry, haematology, urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the Investigator as clinically significant will, if certain requirements are met, be recorded as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that meet the definition of an AE or SAE and are detected during the study or are present at screening and significantly worsen following the start of the study, will be recorded as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied (unless judged by the Investigator as more severe than expected for the subject's condition), or that are present or detected at the start of the study and do not worsen, will not be recorded as AEs or SAEs. The Investigator will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

The Investigator should assess the seriousness and causality (relatedness to the study medication) of all AEs experienced by the subject and this should be documented in the source data. The trial site is responsible for providing full details of AEs/SAEs in the electronic data capture system in the designated eCRF forms continuously during the trial.

11.3.1 Grading of Adverse Event Severity

AEs will be reviewed using the NCI-CTCAE version 5.0 (see Appendix 5 - Common Toxicity Criteria Gradings). **For AEs not specifically graded by the NCI-CTCAE criteria, the criteria in Table 5 will apply**. For each episode, the highest severity grade attained should be reported.

Table 5: Grading of Adverse Event Severity

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

***Instrumental activities of daily living** refer to: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

****Self-care activities of daily living** refer to: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: A **severe** AE is not necessarily a **serious** AE. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the SAE criteria (see list in Appendix 4 - Definition of Adverse Events)

11.3.2 Relationship of Adverse Event to Study Medication

The Investigator will assess the causality/relationship between FP-1305 and the AE and record that assessment in the source data. Causality will be assessed as:

- **Not related:** AE is obviously explained by another cause; OR the time of occurrence of AE is not reasonably related to administration of the IMP
- **Possibly related:** Study drug administration and AE occurrence are reasonably related in time; AND AE is explained equally well by causes other than the IMP
- **Probably related:** Study drug administration and the occurrence of the AE are reasonably related in time; AND the AE is more likely explained by exposure to the IMP than by other mechanisms

11.4 Serious Adverse Events

The Investigator must report AEs that meet the definition of an SAE (see Appendix 4 - Definition of Adverse Events for definition) immediately, or **within 24 hours of the trial site becoming aware of the SAE.**

The AEs defined as serious and which require reporting as an SAE must be reported using either an electronic SAE Form in the eCRF (primary) or a paper SAE Form (back-up method; contact details in the form and on the second page of this protocol). If the trial site personnel are unable to complete

the electronic SAE form within 24 h after receiving information about the event, the initial reporting must be done on the paper SAE report and emailed or fax to Simbec-Orion Pharmacovigilance (within 24 h of awareness). The trial site should report the event in the electronic SAE form of the eCRF as soon as possible after that.

The Investigator Site Staff Signature and Task Delegation Log at each trial site will clearly show delegation of responsibilities regarding SAE reporting. A medically qualified person at the trial site identified on the delegation log with this responsibility must assess the SAE. The Principal Investigator or delegated sub-investigators are responsible for the SAE reporting procedures at the site during the trial and must always sign-off on each SAE (regardless of whether reported using the electronic or paper form) as soon as possible even if other site staff have reported the event on behalf of the investigators.

For all SAEs where important or relevant information is missing, active follow-up must be undertaken. The follow-up information of the SAEs must be reported following the same procedure as for the initial reporting. The follow-up report should describe if the SAE has resolved or is continuing, how it was treated, and whether the subject continued the IMP or whether the IMP administration was permanently discontinued.

11.4.1 Monitoring Pregnancies for Potential Serious Adverse Events

Any pregnancy that occurs in a female subject or the partner of a male subject during the trial, must be reported on the Pregnancy Notification Report form in the eCRF (preferred way) or a paper-based form (back-up; contact details on the form and on the second page of this protocol) and must be immediately sent to Simbec-Orion Pharmacovigilance or within 24 hours of the time the information is known.

Pregnancies must be immediately reported and should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications for up to three months after the birth/termination or if needed, within 1 year after birth where possible and appropriate. Pregnancy in itself is not regarded as an AE.

Consent to report information regarding these pregnancy outcomes should be obtained from the mother. Once consent has been obtained, pregnancy outcomes must be collected for females who took the IMP and the female partners of any males who took the IMP on the Pregnancy Outcome form in the eCRF (preferred way) or a paper-based form (back-up; contact details on the form and on the second page of this protocol) and should be sent to Simbec-Orion Pharmacovigilance immediately or within 24 hours of the time the information is known.

If the pregnancy outcome meets the SAE definition also complete an SAE Form as detailed in Section11.4. It is important to monitor the outcome of any pregnancies of subjects in order to provide SAE data on congenital anomalies, birth defects or spontaneous abortion.

11.5 Adverse Events of Special Interest

Potential autoimmunity has been reported in study subjects after receiving FP-1305. Four study subjects have had hepatic involvement, with a different clinical presentation and associated AE reporting terminology. Some of these events have been graded life-threatening (more details provided in the IB).

An Adverse Event of Special Interest (AESI) is an AE that requires reporting on an expedited basis (The Investigator must report AEs that meet the definition of an AESI immediately, or within 24 hours of the trial site becoming aware of the AESI to Simbec-Orion Pharmacovigilance and on the eCRF), regardless of the seriousness, expectedness, or relatedness of the AE to the administration of the IMP.

In this protocol, the below listed are considered AESIs for FP-1305:

1. Drug induced liver injury defined by Hy's law as:
    - Grade ≥ 2 alanine aminotransferase (ALT) or aspartate transaminase (AST) increase accompanied with
    - Bilirubin elevation > 2 x upper limit of normal (ULN) if baseline value was normal; > 2 x baseline if baseline value was abnormal, without findings of cholestasis or any other reason explaining the combination of increased aminotransferase and serum total bilirubin
2. Any new or worsening of existing autoimmunity after the administration of FP-1305

All AESIs will be followed until recovery or resolution or until the investigator assesses the event to be stable. AESIs will follow the same reporting timeline as that of SAE to pharmacovigilance team.

11.6 AE/SAE Recording and Reporting Period

Details of all AEs will be recorded from the date of consent until the AEs have resolved or no change in the AE status is observed during the post-treatment follow-up period (until Follow-up Visit has been conducted). In circumstances where follow-up visit will not be performed, the follow-up period for AE reporting is 4 weeks from last dose of IMP. If the subject is discontinued from the treatment, the subject must be followed up for open AEs until the AE has resolved, or no change in subject status is observed over the follow-up period. However, all IMP related Grade 3 or 4 AEs must be followed until resolution to Grade 2 or better (for grading see Section 11.3.1).

The investigator is not required to actively monitor subjects for adverse events occurring after the Follow-up Visit has been conducted; however, serious adverse drug reactions occurring after the follow-up period to a subject that has received one or more doses of the IMP should be reported to the Sponsor per the standard SAE reporting process (see Section 11.4) within 24 hours of the investigator or site team member becoming aware of them.

Concomitant medications and procedures associated with Serious Adverse Drug Reactions that occur after subject has withdrawn/discontinued (i.e. after Follow-up Visit) will only be recorded in SAE narrative, and not in the other eCRF pages.

11.7 Reporting to Competent Authorities and Independent Ethics Committees

According to the applicable requirements and Safety Management Plan, any AE that meets the criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) is subject to expedited reporting to the Competent Authorities and IEC(s)/ IRB(s). The reference safety information (RSI) section in the Investigator's Brochure will be used to assess the expectedness of an SAE.

The Development Safety Update Reports (DSUR) will be provided to the Competent Authorities and IEC(s) /IRB(s) responsible for the trial annually. The DSUR will include information on SUSARs, SARs (serious adverse reactions) and other relevant safety findings.

The relevant Competent Authorities and IEC(s)/IRB(s) will be immediately notified if a significant safety issue is identified during the course of the trial.

11.8 Safety Reporting to Investigators

Details of all SUSARs and any other significant safety issues which arise during the course of the trial and any consequences they may have on the trial will be reported to Principal Investigators. If applicable the Investigator will report the SUSAR or significant safety issue to their IEC/IRB. A copy of any such correspondence should be filed in the ISF.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Collection

All relevant data related to safety and efficacy including laboratory values and clinical parameters should be recorded in the medical records and be captured in the eCRF system. The site is responsible for completing the eCRF forms in a timely manner. All data on the eCRFs must be verifiable in the source data/hospital or patient records, unless eCRF data are declared as source data.

12.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Patient Information and Consent Documents, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of eCRFs etc.) are stored in secure archives for 25 years after the end of the trial. However, these documents should be retained for a longer period if required by applicable legal requirements. The Sponsor's approval is required prior to transfer or destruction of the documents.

13 QUALITY MANAGEMENT

This trial is to be conducted according to the ICH harmonised tripartite guideline for good clinical practice E6(R2) and the European Union directive 2001/20/EC to ensure that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (Appendix 3 - WMA Declaration of Helsinki), and that the clinical trial data are credible.
For the trial to start, all required documentation must be approved by the relevant ethical committees and Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the trial.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive ethical committee/competent authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

13.1 Site Set-up and Initiation

All sites will be required to sign a contractual agreement with the Sponsor prior to participation. In addition, all participating Investigators will be asked to sign the necessary agreements and supply a

current curriculum vitae to the Sponsor or representative of the Sponsor. All members of the site research team that will perform study specific activities will also be required to sign the "Site Staff Signature and Task Delegation Log". Prior to commencing recruitment, all sites will undergo a process of initiation. Key members of the site research team will be required to be trained by the Sponsor, or a representative of the Sponsor, covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. The investigators are responsible for ensuring that appropriate training relevant to the study is given to the medical, nursing and other personnel involved in the study. The investigators will also ensure that any information relevant to the conduct of the study is forwarded to the sub-investigators and other relevant study centre personnel. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Sponsor or representative of the Sponsor must be informed immediately of any change in the site research team.

13.2 On-Site Monitoring

A separate Site Monitoring and Management Plan is available where full details of the monitoring activities are described. The trial is conducted according to the GCP and quality standards. Monitors must ensure that the required documentation and trial site training has been done before the site can start enrolling subjects. During the treatment phase, the site(s) will be monitored to ensure protocol adherence and to verify the source data. Any issues in compliance will be reported to the Sponsor.

By participating into this trial, the Investigator(s) and the site(s) conducting this trial will permit trial-related monitoring, audits, Institutional Review Board or equivalent review, and regulatory inspection(s) and provide direct access to source data/documents. A reasonable time must be given for the site(s) to prepare for such activities.

13.3 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Sponsor of any relevant regulatory authority inspections.

13.4 Notification of Serious Breaches

The sites and the Sponsor of the trial will report any serious breaches or protocol/ICH-GCP deviations in accordance with the local laws and current regulations. A "serious breach" is a breach which is likely to effect to a significant degree:

1) The safety and rights of a subject.
2) The reliability and robustness of the data generated in the clinical trial.

Where the Sponsor is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Sponsor in providing sufficient information to report the breach to the relevant Competent Authorities and IEC(s)/IRB(s) where required and in undertaking any corrective and/or preventive action.

14 END OF TRIAL DEFINITION

The end of trial will be the date the overall survival data of the last subject has been collected.

The Sponsor will notify relevant Competent Authorities and IEC(s)/IRB(s) that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

The Sponsor reserves the right to stop the trial at any time on the basis of new information regarding safety or efficacy (e.g., discovery of an unexpected, significant or unacceptable risk to the subjects enrolled in the trial), or if trial progress is unsatisfactory (e.g., failure to enrol subjects at an acceptable rate), or for other valid reasons (e.g., Sponsor decides to suspend or discontinue development of the drug). After such a decision is made, the Investigator must inform all on-trial subjects within 1 week. All delivered trial materials must be collected and all eCRF pages completed to the extent possible.

15 STATISTICAL CONSIDERATIONS

This is an adaptive study conducted in 3 parts with separate objectives. For each part there will be a separate statistical analysis plan (SAP) which includes the full details of the analyses of the endpoints of that part. The SAPs can also have sequel documented subversions in case there are analyses conducted intermittently during some part.

15.1 Trial Population

The trial subject population includes subjects who have advanced (inoperable or metastatic) cutaneous melanoma, pancreatic ductal adenocarcinoma, ovarian cancer, colorectal adenocarcinoma, hepatocellular carcinoma, gallbladder cancer, cholangio-carcinoma, uveal melanoma, gastric (including GE junction) adenocarcinoma, ER+ breast cancer and anaplastic thyroid cancer without standard treatment options available and who adhere to the trial inclusion and exclusion criteria.

For the purpose of analyses the following populations are defined:

Safety population: Includes all subjects who have received any amount of FP-1305

DLT evaluable population: Includes all subjects in Part I who have received at least one dose of FP-1305 and followed up for at least three weeks. Any subject that withdraws, discontinues from the trial or dies not related to treatment prior to the end of the 9-week DLT assessment period will be replaced.

Efficacy evaluable population: Includes all subjects who have received at least one dose of FP-1305 for the first time and has tumour imaging conducted at the baseline, and at least once during the treatment or progress or die due to their disease before the first tumour imaging post FP-1305 administration.

Subjects that re-initiate the treatment: Includes all subjects that have received at least one dose of FP-1305 after re-initiation of the therapy and has tumour imaging conducted at the baseline, and at least once during the treatment or progress or die due to their disease before the first tumour imaging post FP-1305 administration will be analysed for efficacy after the re-initiation in a separate cohort.

15.2 Objectives and Outcome Measures

These are detailed in full in Section 3.

15.3 Analyses of Outcome Measures

15.3.1 Primary Outcome (Part I)

The final model determined MTD, which is the dose level with DLT probability estimated to be closest to the acceptable percentage (target DLT rate) of subjects experiencing a DLT, will be reported with its associated probability of DLT and 90% probability interval. All tolerable doses to be considered will be the MTD and doses below it. The recommended dose for Parts II and III will be selected based on the assessment of changes in immune function, PK and PD data.

15.3.2 Primary Outcome (Part II)

ORR, CBR and irORR will be reported as the proportion of subjects of all evaluable subjects within each tumour type cohort and dose. The 90% confidence intervals for ORR, CBR and irORR will be calculated. Simon's Two-Stage design will be used to evaluate efficacy and decide whether the cohort can be further expanded or not for Part III.

15.3.3 Primary Outcome (Part III)

ORR, CBR and irORR will be reported as the proportion of subjects of all evaluable subjects within each tumour type cohort. The 90% confidence intervals for ORR, CBR and irORR will be calculated. Duration of response is measured from the time of initial response until documented tumour progression, death or dropout.

15.3.4 Secondary and Exploratory Outcomes

15.3.4.1 Monocytes CLEVER-1 positivity

The proportion of CLEVER-1-positive monocytes in the blood total monocyte population will be measured by flow cytometry from blood samples collected over time during the first four cycles. Results will be reported with descriptive statistics. Also explorative statistical analyses will be conducted for the flow cytometry data, if feasible.

15.3.4.2 sCLEVER-1

sCLEVER-1 and its occupancy by FP-1305 in the blood will be measured by immunoassay over time during the first cycles. Results will be reported with descriptive statistics. Also explorative statistical analyses will be conducted for the data, if feasible.

15.3.4.3 Pharmacokinetic Parameters

The serum concentration of FP-1305 will be determined by a validated method according to the assessment schedules. The concentrations will be summarized by visit and the sampling time using descriptive statistics by the dose level. Only subjects who have received the whole dose at each infusion will be used for the repeated PK analysis. The mean concentration will be plotted against the scheduled sampling times. A tabulated summary with descriptive statistics will be given.

15.3.4.4 Immunogenicity

Anti-human FP-1305 antibodies will be assessed analysed by a validated method. Immunogenicity results will be summarized by listing of all available immunogenicity data. The frequency of positivity will be given by dose and cohort. The correlation of AEs and immunogenicity may be examined.

15.3.4.5 Safety

Safety and tolerability will be reported through the assessment of observed adverse events in the subjects. The number of cases and the number of subjects that these cases occurred in will be reported for each event. Drug-related events are reported in a separate table. In addition, both DLTs and drug-related serious adverse events are reported separately in a tabular format, and their seriousness will be assessed based on the NCI-CTCAE classification. AEs are also to be evaluated stratified by dose level and by disease group.

15.4 Analysis of Efficacy Parameters

The proportion of CLEVER-1-positive monocytes in the blood total monocyte population will be measured by flow cytometry from blood samples collected over time during the first four cycles. The results will be reported with descriptive statistics.

Tumour samples collected before and during the treatment will be stained for CLEVER-1. The proportion of CLEVER-1 positive TAMs will be analysed by immunohistochemistry. Macrophage mannose receptor and/or other markers may be used to determine the total content of TAMs. The proportion of CLEVER-1 positive cells prior to and during the treatment will be reported using descriptive statistics. The correlation between circulating CLEVER-1-positive monocytes and CLEVER-1 expression in tumour macrophages will be calculated before and during the treatment. The correlation of the parameters obtained during Cycle 1 with ORR, CRB and irORR rates will also be calculated for subjects included into the ORR/CBR/irORR analysis. The results will be summarized using descriptive statistics. If feasible, exploratory statistical analyses will also be used to describe the associations.

The proportion of lymphocyte subsets (CD4, CD8, their ratio, NK-cells, B-cells and regulatory T-cells), and macrophage HLA expression and myeloid derived suppressor cell populations in circulation will be analysed at given time points with flow cytometry and plotted against the scheduled sampling time. The level of circulating cytokines and chemokines (these may include but are not limited to the following IFNα, IFNγ, IL-1α, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8/CXCL8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17A, IL-18, IL-21, IL-22, IL-23, IL-27, IL-31, TNF alpha, TNF beta, GM-CSF, Eotaxin/CCL11, GRO alpha/CXCL1, IP-10/CXCL10, MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4, RANTES/CCL5, SDF-1α/CXCL12) will be analysed by multiplex assays pre- and post-treatment. Aggregated data (mean and median) from each dose level will be presented using descriptive statistics by tumour type cohort.
ORR, CBR and irORR will be reported as the proportion of subjects of all evaluable subjects within each tumour type cohort. The 95% confidence intervals for the ORR, CBR and irORR will be calculated.

The change in LDH, LDL and OxLDL, CRP, CA-125 (OC subjects), CA19-9 (PDAC, gallbladder cancer, cholangiocarcinoma, gastric adenocarcinoma subjects), CEA (CRC, ER+ BC, gastric adeno-carcinoma subjects), CA-15-3 (ER+ BC subjects) and AFP (HCC subjects) levels in the subjects pre- and post-treatment will be reported with descriptive statistics.

The correlation of the response according to RECIST 1.1 defined responses (CR/PR/SD/PD) with the immune cell profile, the level of circulating cytokines and chemokines, CLEVER-1 on circulating monocytes, and possible genetic analyses during the first four cycles of treatment will be reported using descriptive statistics. If feasible, exploratory statistical analyses will also be used to describe the associations.

The receptor occupancy of FP-1305 on the circulating monocytes during Part I and in some subjects during Part II will be analysed using flow cytometry and will be plotted against scheduled sampling times. Aggregated data (mean and median) from each dose level will be presented by tumour type cohort. The results will be summarized using descriptive statistics.

Free sCLEVER-1 in the circulation will be measured with immunoassay.
Overall survival data, including but not limited to the six-month, one-year and two-year survival rates will be reported for each cohort, and will be analysed using the Kaplan-Meier method and cox-modelling where appropriate.

Progression free survival including but not limited to the six-month, one-year and two-year survival rates will be reported for each tumour type cohort and will be analysed using the Kaplan-Meier method and cox-modelling where appropriate.

15.5 Planned Interim Analysis

There is no predefined interim analysis. Interim analyses on safety and efficacy or on PK, immunogenicity, and selected biomarkers may be provided on ongoing basis prior to completion of the trial in order to expedite conclusions and to support trial presentations or publications.

15.6 Planned Main Analyses

Part I
The main analysis for determining the recommended dose to be expanded upon will take place once all subjects in part I have been recruited to trial and have been followed-up for the 9-week DLT assessment period.

Part II
Each cohort will be analysed when ten evaluable subjects have been accrued and treated with the selected dose. Subjects from Part I can be included into the cohort of ten subjects if they have been treated with the selected dose.

Part III
Each cohort that is continued after the analysis of Part II will be analysed when 29 evaluable subjects have been accrued and treated with optimal dose or until the required 4 responders are reached. The cohort can continue accruing subjects if the stopping rule is not met. The final analysis of each cohort is when the particular cohort has been considered complete.

15.7 Power Calculations

The operating characteristics of the TITE-CRM will be assessed to assure the design is well calibrated for determining the MTD. Fine-tuning of the model to tailor to the trial's requirements will be aided with the use of the Dose-Transition Pathways, which maps out in advance how the model will recommend doses for all permutations of DLT outcomes for the initial subjects (Yap et al, 2017). Details of the TITE-CRM is presented in the corresponding statistical analysis plan. Part II and Part III are based on adaptive Simon's Two-Stage design, with the following assumptions Type I error rate (α; one-sided) 0.05, power 0.80, response probability in the palliative treatment 5% (alternative option for these subjects) and response in the trial treatment 20%, 10 subjects in each cohort with at least one subject that demonstrates clinical benefit (CBR by RECIST 1.1 criteria) in the Part II is needed to conclude that the cohort may be expanded. Additionally, data from Part II will be used to determine CLEVER-1 positivity in each of the cohorts. If it is possible that cohorts can be divided in

the CLEVER-1 positive and CLEVER-1 negative groups, both subgroups will be expanded in Part III so that 10 subjects in each group are recruited. In case there are 10/10 non-responders in either of the subgroups, then the recruitment will continue only in the other subgroup with responders. The recruitment can continue within that subgroup until the planned maximum of 29 subjects (or until the required 4 subjects that demonstrate clinical benefit are reached). If the subgroups cannot be defined, the Part III continues with the original cohorts having 1 responder in the cohort. In case there are clearly more negative than positive subjects in some cohort, and also clear difference in the response, the DMC will evaluate the data and decide further cohort expansions.

If the desirable response is obtained in Part III of the trial the cohort(s) may be further expanded.

16 ACCESS TO SOURCE DATA AND RELATED DOCUMENTS

By participating into this trial, the Investigator(s) and the site(s) conducting this trial will permit trial-related monitoring, audits, Institutional Review Board or equivalent review, and regulatory inspection(s) and provide direct access to source data/documents. A reasonable time must be given for the site(s) to prepare for such activities.

17 TRIAL ORGANISATIONAL STRUCTURE

17.1 Sponsor

The Sponsor of the trial is Faron Pharmaceuticals. The Sponsor may delegate duties to trial sites and to contract research organizations.

17.2 Data Monitoring Committee

The DMC will be composed, as a minimum, of the designated investigators and other specialists with relevant expertise and independent of the trial will be invited to be members of the committee. Key supportive roles in coordinating the meetings and producing the required data include the Sponsor's Chief Medical Officer and Simbec-Orion's (CRO) Medical Expert and Study Statistician.

The committee will formally review toxicity and other relevant data including the recommendation from TITE-CRM at any time DLT has been observed and after completion of the Part I and further on in Part II according to 3+3 design.The DMC will issue recommendations to dose-escalation and optimal dose(s).
If applicable, the committee may recommend to

- stop dose escalation, for example if a plateau in biomarker changes has been identified, or
- add one or more dose escalation cohort(s) if the highest dose is reached in the absence of DLT and a plateau in biomarker changes has not been identified or
- add one or more intermediate dose level(s)
- add three additional subjects to one or more dose levels below the MTD / highest tested dose level to obtain more data to inform dose selection for Part II and III, and when deemed necessary, recommend to add even further subjects to any defined dose level(s) in Part I
- increase the post-dose monitoring time for the study subjects
- discontinue enrolment in a cohort to ensure the best benefit of the subjects
- modify dosing for ongoing subjects if indicated by accumulated data

All decisions will be documented in the form of minutes. Addition of new dose escalation cohorts will require the competent authority approval if this new cohort is higher than the maximum dose in the protocol.

17.3 Finance

The Sponsor will make contracts with trial sites and contract research organizations.

18 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 (website: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/; Appendix 3 - WMA Declaration of Helsinki).

The trial will be conducted in accordance with the the European Union directive 2001/20/EC, data protection regulation (Regulation (EU) 2016/679), local laws, and the ICH GCP E6(R2). This trial will be carried out under a Clinical Trial Authorisation in accordance with local regulations. The protocol will be submitted to and approved by the corresponding ethical committees.

Before any subjects are enrolled into the trial, the Principal Investigator at each site is required to obtain corresponding approval. Sites will not be permitted to enrol subjects until written confirmation of approval is received.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual subjects.

Evaluation of the anticipated benefits and risks of the IMP and with regards to the participation of a subject is conducted requlary. This evaluation is performed, at a minimum, annually in association with the IB annual update/review, if accumulated data does not indicate a need for more frequent evaluation.

19 CONFIDENTIALITY AND DATA PROTECTION

Personal information of the study subjects collected during the trial will be processed in accordance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation, GDPR) and all applicable local laws.

All trial findings and documents will be regarded as confidential. The Investigator and members of their research team must not disclose any information without prior written approval from the Sponsor. The Investigator must maintain documents not for submission to the Sponsor in strict confidence. In the case of specific issues and/or queries from the Regulatory Authorities, it will be necessary to have access to the complete trial records, provided that subject confidentiality is protected.

Subjects will be identified on the eCRF and other documents submitted to the Sponsor or Sponsor's representative by their trial subject number. Documents that identify the subject must not to be submitted to the Sponsor and must be maintained in confidence by the Investigator.

The Investigators (and appropriately authorised staff) will be given access to an online web-based electronic data-capture system that is compliant with US Food and Drug Administration Title 21 Code of Federal Regulations Part 11. This system is specifically designed for the collection of clinical data in electronic format. Access rights to the electronic data-capture system will be carefully controlled and configured according to each individual's role throughout the trial. Only the Investigator and authorised staff will be able to enter and correct data in the eCRF.

The eCRF should be completed for each subject included in the trial and should reflect the latest observations on the subjects participating in the trial. Therefore, the eCRF is to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerised data-check programs and manual checks will identify any data discrepancies for resolution. Corresponding queries will be generated in the system and the site will be informed online about new issues to be resolved. All discrepancies must be resolved online directly by the Investigator or by staff authorised to do this by Delegation of Authority.

The Investigator will be required to electronically sign off the clinical data recorded in the eCRF.

20 PUBLICATION POLICY

Any manuscript, abstract or other publication or presentation of results or information arising in connection with the trial (including any ancillary trial involving trial subjects) must be prepared in conjunction with the trial Sponsor and must be submitted to the Sponsor for review and comment at least 45 days prior to submission for publication or presentation. No single centre or groups of centres may publish individually. The Sponsor will review the communications for accuracy to avoid potential discrepancies with submissions to health authorities, verify that confidential information is not accidentally disclosed, and provide any relevant supplementary information. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. The Sponsor may delay such submission by a maximum of 90 days if it reasonably believes that publication of results may compromise its intellectual property rights or may insist that such information or data is removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

The original eCRF pages and all data generated during the trial under this protocol will become the property of the Sponsor.

The Sponsor may announce quality-assured summary data in order to comply with the requirements of financial regulatory authorities, while ensuring so far as possible that such announcements will not compromise the Investigators' ability to publish the data in appropriate scientific forums. Authorship of communications arising from the trial-related data and subsequent analysis may include members from the contributing site(s) including basic research laboratories and Sponsor's personnel.

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22 APPENDIX 1 - RECIST CRITERIA

The following contains excerpts from the RECIST version 1.1 plus trial specific instructions.
A free copy of the revised guidelines is available from https://recist.eortc.org/recist-1-1-2/
http://www.eortc.be/recist/default.htm
(Eisenhauer *et al*., 2009)

Measurability of Tumour Lesions at Baseline
Only patients with measurable disease at baseline should be included in Parts II and III. Measurable disease is defined by the presence of at least one measurable lesion. At baseline, tumour lesions will be categorised as follows:

- Measurable
- Non-measurable

Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable) and 20 mm by chest X-ray. For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by a CT scan (at baseline and during treatment, only the short axis will be measured and followed).

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to >15 mm short axis) and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumour lesions that are situated in a previously irradiated area are not considered measurable.
The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation using callipers (or a ruler) if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Specifications by Methods of Measurements
The same method of assessment and the same technique should be used to characterise each identified and reported lesions at baseline, during treatment and at the post-treatment assessment. Image-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment. CT is the best currently available and reproducible method for measuring target lesions selected for response assessment. Investigators should utilise the best available CT imaging technique available to them for determining response and PFS of patients participating in the MATINS trial.

Tumour Response Evaluation

Baseline Documentation of "Target" and "Non-target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as "target" lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate, reproducible, repeated measurements.
A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterise the objective tumour response.

All other lesions (or sites of disease) should be identified as "non-target" lesions and should also be recorded at baseline. Measurements of these lesions are not required but these lesions should be followed as 'present', 'absent' or in rare cases 'unequivocal progression' and recorded.

Response Criteria

A. Evaluation of Target Lesions

Response Category	**Description**
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to this, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more lesion is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started

B. Evaluation of Non-target Lesions

Response Category	**Description**
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [1]

Notes:

1. To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

D. Overall Responses for all Possible Combinations of Tumour Responses in Target and Non-target Lesions With or Without the Appearance of New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response (CR)	CR	No	CR
Complete response (CR)	Non-CR/non-Progressive disease	No	PR
Complete response (CR)	Not evaluated	No	PR
Partial response (PR)	Non-Progressive disease	No	PR
Stable disease (SD)	Non-Progressive disease	No	SD
Not all evaluated	Non-Progressive disease	No	Not evaluable (NE)
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

23 APPENDIX 2 - IMMUNE-RELATED RESPONSE CRITERIA

The following contains immune-related response criteria using unidimensional measurements. It is a modification of RECIST version 1.1 and is based on the publication by Nishino et al. Clin Cancer Res. 2013:19: 3936–3943 plus trial specific instructions.

Measurability of Tumour Lesions at Baseline
Follow the definitions from RECIST 1.1.

Baseline Documentation of "Target" and "Non-target" Lesions
Follow the definitions from RECIST 1.1. However, lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumour Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

Recording of Target and New Measurable Lesion Measurements
The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Unidimensional measurements are used. Measurements of all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into TMTB at follow-up. Baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

New measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions, because there will be a greater impact of the TMTB %-increase by these larger lesions for irPD.

Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the TMTB, and one combined assessment provided.

Response Criteria
A. Evaluation of Target Lesions

Response Category	Description
irCR	Complete disappearance of all target lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation by two consecutive observations not less than 4 weeks apart is required.
irPR	Decrease of ≥ 30% in TMTB relative to baseline. Confirmation by two consecutive observations not less than 4 weeks apart is required.
irProgressive disease	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir. Confirmation by two consecutive observations not less than 4 weeks apart is required.
irSD	No irCR or irPR in the absence of irProgressive disease.

Notes:

1. To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease and symptoms such that, even in presence of irSD or irPR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

B. Evaluation of Non-Target Lesions

Response Category	Description
irCR	Disappearance of all non-target lesions
irProgressive disease	Unequivocal progression of non-target lesions

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

D. Overall Responses for All Possible Combinations of Tumour Responses in Target and Non-Target Lesions with or without the Appearance of New Lesions

Target Lesions	Non-target Lesions	Overall Response
irCR	irCR	irCR
irCR	non-irProgressive disease	irPR
irPR	irCR	irPR
irPR	non-irProgressive disease	irPR
irSD	non-irProgressive disease	irSD
Any	irProgressive disease	irProgressive disease

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

Frequency of Tumour Re-evaluations

For the trial, clinical response rate, disease control rate (CR+PR+SD), PFS and duration of response will be evaluated by CT or MRI scan of the abdomen at baseline. Repeat imaging must be performed with the same method and will be performed according to schedule of assessment.

24 APPENDIX 3 - WMA DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.
    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/;

25 APPENDIX 4 - DEFINITION OF ADVERSE EVENTS

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

1) Results in death
2) Is life-threatening [1]
3) Requires hospitalisation [2] or prolongation of existing inpatients' hospitalisation
4) Results in persistent or significant disability or incapacity
5) Is a congenital anomaly/birth defect
6) Or is otherwise considered medically significant by the Investigator [3]

Comments:
The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

[1] Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

[2] Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus, hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

[3] Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An SAE that is suspected to be associated with the use of the IMP and unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

26 APPENDIX 5 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the NCI-CTCAE version 5.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm;

27 APPENDIX 6 - ECOG PERFORMANCE STATUS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.

28 APPENDIX 7 - NYHA CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

The Criteria Committee of the New York Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th Ed.) . Boston: Little, Brown & Co. pp. 253-256.