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 code: MATINS

Phase I/II study

STATISTICAL ANALYSIS PLAN

FOR PART I

AMENDMENT CREATED FOR DATABASE LOCK

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1 Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
CA	Cancer antigen
CBR	Clinical benefit rate
CEA	Carcinoembryonic antigen
CLEVER-1	Common lymphatic endothelial and vascular endothelial receptor-1
CRC	Colorectal adenocarcinoma
CRP	C-reactive protein
DLT	Dose Limiting Toxicity
FAS-E	Full analysis set for efficacy
FAS-S	Full analysis set for safety
HCC	hepatocellular carcinoma
irORR	Immune-related objective response rate
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MedDRA	Medical dictionary of regulatory authorities
OC	Ovarian cancer
ORR	Objective response rate
PDAC	Pancreatic ductal adenocarcinoma
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per protocol set
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SD	Standard deviation
SAE	Serious adverse event
TEAE	Treatment emergent adverse event
TITE-CRM	Time-to-event continual reassessment method

2 General remark

This is a statistical analysis plan (SAP) for the Part I of the trial. For the dose escalation part conducted with TITE-CRM methodology, there was a separate SAP finalized March 29th 2019. So far there has been no DLT events in the study, so this analysis plan is concerning all the remaining variables of the study. An original version of this SAP was finalized before the Data Monitoring Committee (DMC) meeting held March 27th 2020, as the dose response analyses of current raw database were presented and evaluated in that meeting. This is an amendment version of SAP created before the actual database lock for the Part I. Changes and updates to the original SAP will be summarized in chapter 17.

3 Study objective(s) for Part I

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 (HCC), pancreatic, colorectal (CRC) or ovarian cancer (OC) or melanoma without standard treatment options

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 Objective Response Rate (ORR) and immune-related ORR (irORR) in each cohort of different tumour type

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 (OC subjects), CA19-9 (PDAC, cholangiocarcinoma subjects), AFP (HCC subjects), Carcinoembryonic antigen (CEA) (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

4 Design and type of the study

This is an open label, three-part, 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. This interval is called a cycle. In part I approximately 30 subjects are planned to be enrolled, in part II maximum of additional 90 subjects will be enrolled, in Part III additional subjects will be enrolled so that the total number of subjects in the whole trial is up to 650.

5 Study variables

The following variables will be evaluated for Part I of the study:

The demographic and baseline variables

Gender, age at entry, race, country, weight, height, BMI, medical history, concomitant medications/therapies, CMV infection status and pregnancy test (females of child-bearing potential), and HIV serology.

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

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 (C_{max}), trough concentration (C_{min}), area under the plasma concentration versus time curve (AUC), clearance, volume of distribution, and terminal halflife ($t_{1/2}$) 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 mean

fluorescence intensity 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, MCP-4, MDC, MIP-1α/CCL3, MIP-1β/CCL4, TARC) 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.

6 Sample size considerations

For Part I 30 subjects were planned. The total number of patients dosed was 30.

7 Statistical hypotheses

There are no statistical hypothesis for Part I as the main focus was in the dose escalation using the TITE-CRM methodology.

8 Analysis datasets

Following analysis populations have been described in the protocol:

Safety population: Includes all subjects who have received any amount of CLEVER-1 antibody FP-1305. This formulates the Full Analysis Set for Safety (FAS-S).

DLT evaluable population: Includes all subjects in Part I who have received at least one dose of CLEVER-1 antibody 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 CLEVER-1 antibody 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. This formulates the Full Analysis Set for Efficacy (FAS-E).

Subsets used for efficacy evaluation can be formulated for the exploratory dose response analyses of Part I data, based on the clinical reasoning concerning the surrogate variables and target patient population for each disease cohort of the Part II and Part III of the study. Patient classification will be summarized in a separate document for complete and locked Part I data.

9 General statistical considerations

Summary statistics will include at least the number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequencies and percentages for categorical variables. All data collected will be listed by subject.

In the statistical analyses a p-value less than 0.05 will be considered as an indication of statistical significance. If not stated otherwise, all tests will be performed as two-sided tests and two-sided 95% confidence intervals will be produced. Missing values will not be imputed in the analyses.

This is Part I of the study with main emphasis on the definition of safe tolerable doses for remaining parts of the study. Another objective is to define preliminary information of the dose response concerning efficacy and to provide decision support for defining which doses would be included in the Part II of the study.

9.1 Handling of drop-outs or missing data

Missing values will not be imputed.

9.2 Interim analyses and data monitoring

Exploratory dose response analyses will be conducted for the DMC meeting on 27th March 2020, using the current raw database. These analyses will be replicated once the Part 1 data is complete and locked for analyses.

9.3 Examination of subgroups

Disease types will be presented along the results and some analyses will be presented for the colorectal cancer patients separately.

10 Demographic and other baseline characteristics

Number of patients enrolled into the study at screening and the reasons for screening failures will be summarized. The number of patients entering and completing the study will be summarized. All patients discontinuing the study will be summarized together with the reason(s) for discontinuation.

Demographic and baseline characteristics will be summarized by treatment using descriptive statistics. Following variables will be analysed.

- Gender
- Age at entry
- Race
- Weight

- Disease type (cohort)
- Medical history
- Concomitant medications/therapies
- Symptomatic cytomegalovirus infection
- Pregnancy test (females of child-bearing potential).

Medical history and concomitant medications/therapies will be presented only by frequency and subject count-based tables according to MedDRA/WHO Anatomical Therapeutic Chemical (ATC) classification.

11 Extent of exposure and compliance

Treatment exposure, study duration and treatment compliance will be summarised by diseases types using descriptive statistics.

12 Analysis of dose response

The primary objective of the part I of the study was to determine the tolerability of the used doses. As a secondary objective it is to assess the preliminary efficacy of FP-1305 monotherapy by ORR and irORR in each cohort of different tumour type. The amount of data is however quite limited especially considering the cohorts. Also, there has been 5 dose levels used in Part I and possibly not all are in the effective range. Thus, the main interest regarding the efficacy outcomes is to explore the dose response regarding efficacy, besides the dose response regarding toxicity.

ORR is confirmed only at Cycle 7 so many patients from Part I are not continuing in the study until that. Thus, several other variables will be of interest in addition to ORR. (At least) the following variables will be used for dose response analysis:

Key efficacy response variables (in hierarchical order)

1) Clinical response (ORR) at Cycle 4 (confirmed C7), and all other response evaluation results at all follow-up time points
2) Cancer specific markers (e.g. CEA in colorectal cancer, CA19-9 in PDAC, cholangiocarcinoma, LDH in OC), change over time in the markers

3) IFN gamma % change, and absolute change from baseline in Cycle 1 (including a tabulation of 1.3-fold and 2-fold increases)

4) Inflammatory markers IP-10, % change, and absolute change from baseline in Cycle 1 (including a tabulation of 1.3-fold increase), IL-6 (1.1-fold and 1.3-fold decrease), IL-8 (1.1 and 1.3-fold decrease) in Cycle 1

Exploratory efficacy response variables

* NK cells % change from baseline in Cycle 1 (including a tabulation of 1.2-fold and 1.3-fold increase)

* CD8/CD4 ratio, % change from baseline Cycle 1 (including a tabulation of 1.2-fold and 1.3-fold increase)

* CD8 % change from baseline Cycle 1 (including a tabulation of 1.2-fold and 1.3-fold increase)
* CD4 % change from baseline Cycle 1 (including a tabulation of 1.2-fold and 1.3-fold increase)
* B cells, % change from baseline Cycle 1 (including a tabulation of 1.2-fold and 1.3-fold increase)
* P-albumin, LDL and CRP (visual inspection)
* Receptor occupancy and monocytes (RO assay) in Cycle 1 (data not yet available)

In the toxicological dose escalation TITE-CRM methodology was applied. For the 30 subjects included in the study there are no DLT events. Thus, the dose response evaluation is based on the efficacy measurements. Several different approaches were explored and evaluated, which use similar kind of approach than TITE-CRM, i.e. using Bayesian framework of analyzing efficacy (combined with toxicity or alone) dose response. As suggested by Zhang et al (2014), parametric and semi-parametric logistic and non-parametric isotonic regression models will be applied to the dichotomic dose response data in order to get posterior estimates of the proportion treatment responding patients in each dose cohort. These calculations can be done for part of the above biomarker responses in addition to ORR, based on the clinical judgement of the most relevant markers and cut-off values.

For the combined efficacy and toxicology analysis the efficacy-toxicity trade-off (based on Thall P, Cook J 2004) was explored as it can be implemented using R package stan_efftox. However, it was not seen to be optimal for this case as the analysis is retrospective and the dose response is not necessarily monotonic here. However, these results can be obtained in order to compare those with the results using other approaches (described above), if feasible.

Visualization of the biomarker data for both individual and mean values (by doses) and descriptive statistics by dose and time point will be created for all biomarkers listed above. In addition, for the continuous response variables (basically all of the above listed biomarkers) linear regression models, and mixed models for repeated measurements will be fitted to evaluate and test the effect of dose (plain or quadratic) and providing estimates for the biomarker effects in each timepoint. This is also very relevant for the exploration of the association of biomarker responses and tumour responses. If there is a connection between dose and biomarker response, and furthermore a connection between biomarker and tumour response, that could be important finding concerning the dose response pattern.

Furthermore, also the concentration and PK parameters results will be evaluated, and this information is incorporated in the dose response analyses (to the extent possible based on the availability of PK data). The analyses will be performed for the DMC meeting scheduled for March 27th 2020, and updated when the Part 1 database is locked.

12.1.1 Efficacy variable

The ORR to the treatment will be determined by tumour imaging according to RECIST 1.1 (as specified in study protocol). Proportion of patients responding to treatment (including Partial, Complete responses) will be summarised by dose (and disease type).

The CBR is the proportion of subjects that have a complete response, partial response, or stable disease. The irORR will also be calculated.

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.

13 PK variables

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 (C_{max}), trough concentration (C_{min}), area under the plasma concentration versus time curve (AUC), clearance, volume of distribution, and terminal halflife ($t_{1/2}$) for each dose level will be determined.

14 Other variables

Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up.

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 mean fluorescence intensity will be reported.

15 Analysis of safety and tolerability

All subjects in the FAS-S analysis set (all patients receiving study treatment) will be included in the safety and tolerability analysis.

15.1 Dose limiting toxicities

The primary variable for the dose escalation purpose, the occurrence of dose limiting toxicities (DLT) was planned be summarised by dose level. In case applied, the planned TITE-CRM would be summarized with all information about dose selection process.

15.2 Adverse events

All recorded adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent adverse event (TEAE) is defined as an AE that begins or

worsens in severity after at least one dose of study drug has been administered. Non-treatment emergent AEs are listed only.

TEAEs will be summarized using frequency and subject based tables. TEAEs will be tabulated by dose cohort, system organ class (SOC), preferred term (PT), causality and severity. For analysis purposes, each subject will also be categorized by the maximum severity reported for a given TEAE (similar PT) and these will be tabulated by maximum severity. If feasible, the AEs will be summarised by treatment cycles and by diseases type.

Serious adverse events (SAEs) and AEs leading to discontinuation will be summarized by treatment groups.

15.3 Laboratory safety variables

Part of the laboratory safety measurements will be used for dose response evaluation and reported along that. For completeness, the descriptive statistics of all safety parameters will be reported as a part of safety data also. Safety labs collected are listed in the schedule of assessments for Part 1 (see appendix). Aggregated data (mean and median) from each dose level will be presented using descriptive statistics. In addition, shift tables (within, below and above the normal range) will be provided for each parameter in relation to the maximum change from baseline from D0 over the complete 30-day follow-up period.

15.4 Other safety variables

Other safety variable to be analysed are vital signs (body temperature, blood pressure, heart rate) and physical examination.

Absolute values and changes from baseline are both summarized. In addition, the maximum change from baseline over the 30-day follow-up period will be calculated for each patient and summarized. Vital signs summaries will be in terms of mean, median, SD, minimum and maximum.

Physical examination covering all the major organ systems will be performed at screening and pre-treatment within each cycle. These will be summarized by treatment groups and visits using frequency and percentage of normal/abnormal observations.

16 Completion and premature discontinuation

Completion and premature discontinuation will be listed. The reasons for premature discontinuation will be presented.

17 Deviations from the analyses planned in the study protocol

There are no major deviations in the statistical analysis plan from the analyses planned in the study protocol. The analyses defined in this SAP are exploratory.

18 Execution of statistical analyses

Statistical analyses will be performed by 4Pharma Ltd.

19 Hardware and software

Statistical analysis, tables and patient data listings will be performed with SAS® version 9.4 or later for Windows (SAS Institute Inc., Cary, NC, USA). R will be used for part of the dose response analyses.

20 References

Clinical Study Protocol (FP2CLI001), Final Protocol version 06 (28 November 2019), Faron Pharmaceuticals Ltd.

Thall P, Cook J (2004). "Dose-Finding Based on Efficacy-Toxicity Trade-Offs."Biometrics,60(3), 684–693.

Zang, Y., Lee, J. and Yuan, Y. (2014) Adaptive Designs for Identifying Optimal Biological Dose for Molecularly Targeted Agents, *Clinical Trials*, 11, 319-327.

21 Appendices

21.1 Study flow chart

Table 1: Schedule of Assessments for Part I

	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															
Trial drug 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			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
PK&ADA																
PK sampling[6]		X		X	X	X	X	X	X	X	X		$X^{C3, C4}$			

	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		
ADA sampling[7]		X											X			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}			
P-LDH		X											X			X
P-LDL		X											X			X
S-AFP (HCC)		X											X			X
P-CRP		X											X			X
S-CA-125 (OC)		X											X			X
S-CA19-9 (PDAC/ cholangiocarcinoma)		X											X			X
S-CEA (CRC)		X											X			X
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}			

	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		
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		X	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] For all cycles, Vital signs to be taken before IMP administration, and every 20 minutes for 1 h (3 additional readings) thereafter (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 measurement), and in Cycle 1 5 h after IMP infusion completion

[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] Pre dose 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: P-glucose, P-calcium, P-sodium, P-potassium, P-chloride, P-creatinine, P-ALT, P-ALP, P-AST, P-CK, P-total bilirubin, P-albumin

[11] Endocrine panel 1: P- or S-Cortisol (same method throughout the study), P-lipase and P-amylase (pancreas specific) on cycles 1, 4 and 8 and when clinically indicated

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

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

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

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

[16] Post IMP administration timepoints in Cycles 1 and 2 D8 (+/-24 h) and D15 (+/- 24 h)

[17] Post IMP administration timepoints in Cycle 1 D5 (+/- 4 h). Genetic analyses from peripheral blood cells may be performed

[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. The biopsies or archival material will be assessed by immunohistochemistry (IHC) for T-cells and monocytes, and genetic analyses may be performed.

[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

[21] Brain imaging (CT) for exclusion of CNS metastasis. Routine diagnostic image (CT/MRI) can be used if available within two weeks prior to first dose.

[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.

[23] Follow-up visit will be performed 3 weeks (+/- 1 week) after Cycle 17 IMP administration (or within 3 weeks of the decision to discontinue the IMP in case subject discontinues before Cycle 17). 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.

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SAP MATINS amendment for Part 1 DB lock 22.06.2021 final clean - Copy

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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 code: MATINS

Phase I/II study

STATISTICAL ANALYSIS PLAN

FOR PART II (ORIGINALLY ENROLLED COHORTS)

Signatures:

Statistical Analysis Plan was prepared by:

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Study Statistician
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Jul 6, 2022
Date

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Date

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1 Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
CA	Cancer antigen
CBR	Clinical benefit rate
CEA	Carcinoembryonic antigen
CI	Confidence interval
CLEVER-1	Common lymphatic endothelial and vascular endothelial receptor-1
CR	Complete response
irCR	Immune-related Complete response
CRC	Colorectal adenocarcinoma
CRP	C-reactive protein
DCR	Disease control rate
DLT	Dose Limiting Toxicity
FAS-E	Full analysis set for efficacy
FAS-S	Full analysis set for safety
HCC	hepatocellular carcinoma
irORR	Immune-related objective response rate
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOQ	Lower level of quantification
MedDRA	Medical dictionary of regulatory authorities
NCA	Non-compartmental analysis
OC	Ovarian cancer
ORR	Objective response rate
PDAC	Pancreatic ductal adenocarcinoma
PD	Progressive disease
PK	Pharmacokinetics
PPS	Per protocol set
irPR	Immune-related Partial response
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SD	Stable disease

SAE	Serious adverse event
TEAE	Treatment emergent adverse event

2 General remark

This is a statistical analysis plan (SAP) for the Part II of the trial. For Part I, there were separate SAP's for the dose escalation part conducted with TITE-CRM methodology (finalized March 29th 2019) and for the all other remaining variables (finalized March 26th 2020). This SAP version is created at the time when for the originally enrolled Part II cohorts have finished their treatment and these subjects' data (12 cohorts of ten subjects, n=120) will be reported and compiled for TLF package. For some purposes, also the part I subjects' data (n=30) will be used to analyze the full cumulative data of the study so far.

Since the study still is ongoing a so-called soft lock of the study data will be made. It should be noted that protocol deviations will not be locked at this time.

3 Study objective(s) for Part II

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

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

Exploratory Objectives for Part II

- To assess the amount of soluble CLEVER-1 (S-CLEVER-1) in the subjects prior to treatment
- To characterize the receptor occupancy of FP-1305 on S-CLEVER-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

4 Design and type of the study

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 preliminary efficacy of repeated doses of CLEVER-1 antibody FP-1305 administered in three-weeks intervals (Q3W) in subjects with cutaneous melanoma, pancreatic ductal adenocarcinoma, ovarian cancer, colorectal adenocarcinoma, hepatocellular carcinoma, gallbladder cancer or cholangiocarcinoma, uveal melanoma, gastric (including GE junction) adenocarcinoma, ER+ breast cancer and anaplastic thyroid cancer.

In Part I 30 subjects were enrolled as planned. Part II consists of 10 enrolled subjects per cancer type (10 disease cohorts) at each selected Part II dose (1 mg/kg for all cohorts and 0.3 mg/kg, 1.0 mg/kg and 3.0 mg/kg for colorectal adenocarcinoma cohort) and dosing scheme (Q3W for all cancer types, Q2W and Q1W for selected cancer types). In addition to these, the study recruited cohorts for Q3W dosing of 3.0 mg and 10.0 mg for Cutaneous melanoma and Gastric adenocarcinoma, and also a cohort testing a higher dose (30.0 mg/kg) for any cancer cohort. Part III additional subjects will be enrolled based on the continuation rules set in the protocol (cohorts with at least 1/10 Clinical Benefit Rate will be expanded to total of 29 evaluable subjects). Thus, it is estimated that the total number of subjects in the whole trial can be up to 700 enrolled subjects.

In the study protocol, the study drug is set to be administered Q3W intervals. Based on the analysis of the PK, receptor occupancy and pharmacodynamic during the Q3W administration, it was deemed necessary to study more frequent dosing. With a country specific addendum, Q2W and Q1W dosing intervals are implemented into Part II. These are evaluated as separate Part II expansion cohorts.

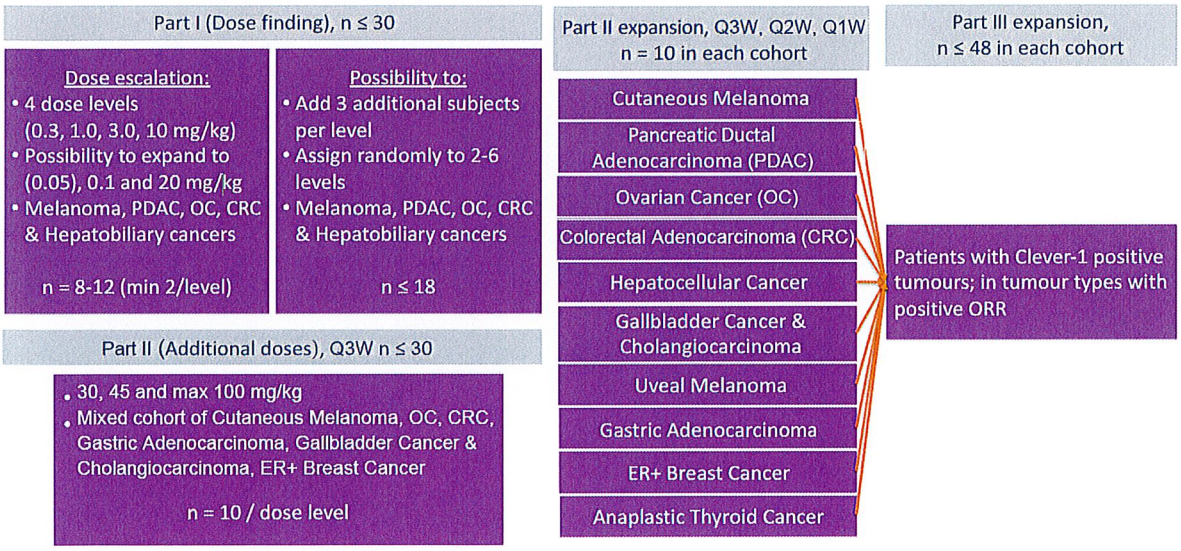

Figure 1. Study design

5 Study variables

The following variables will be evaluated for Part II of the study:

The demographic and baseline variables

Gender, age at entry, race, weight, height, medical history, concomitant medications/therapies (including prior cancer therapies), CMV infection status and pregnancy test (females of child-bearing potential), ECOG performance status, baseline tumour imaging results and HIV serology.

Part II

Primary outcome measure

- 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 dose limiting toxicity (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 (C_{max}), through concentration (C_{min}), area under the serum concentration versus time curve (AUC), clearance, volume of distribution, and terminal halflife ($t_{1/2}$) 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 predictive genetic, cellular and other 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.

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.
    - Clever-1 anti-FP-1305 MFI
    - Clever-1 anti-9-11 MFI
    - Anti-PD-1 MFI
- Anti-CTLA-4 MFI 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.
    - Clever-1 anti-FP-1305 % of cells
    - Clever-1 anti-9-11 % of cells

- S-CLEVER-1 and its blockage will be determined by measuring the amount of S-CLEVER-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/mm^2 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.
    - In addition to CD8, also CD4, CD163 and FoxP3 positive cells have been measured
- 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 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-1 α /CCL3, MIP-1 β /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.

6 Sample size considerations

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 proceed from one part to the next part). It is estimated that the total number of subjects in the whole trial is up to 700.

7 Statistical hypotheses

Expansion of each cohort to Part III of the trial is based on the predefined rule applying Simon's 2-stage design. Clinical benefit ratio (CBR) of 1/10 is needed in order to expand the cohort up to a total of 29 subjects per cohort.

8 Analysis datasets

Following analysis populations have been described in the protocol:

Safety population: Includes all subjects who have received any amount of FP-1305. This formulates the Full Analysis Set for Safety (FAS-S).

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.

Regarding Part II, the first three subjects recruited to the unique cohort are included in the DLT evaluable population. The amount is expanded to six subjects if there is one DLT event in the first three subjects. The following cohorts are investigated: Q3W cohorts at dose levels that have not previously been tested in Part I, Q2W cohorts at each new dose level and Q1W cohorts at each new dose level. DLT assessment period in Part II is 4 weeks from the first dose of FP-1305.

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. This formulates the Full Analysis Set for Efficacy (FAS-E).

In the FAS populations also Part I subjects will be included.

9 General statistical considerations

Summary statistics will include at least the number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequencies and percentages for categorical variables. All data collected will be listed by subject.

In Part II, the disease group or dosing cohorts of 10 subjects will be presented separately as also the Simon's design rule will be applied separately for each cohort. In addition, the cohorts using originally recommended dosing regimen for Part II, Q3W (1.0 mg for all cohorts and 0.3 mg/kg and 3.0 mg/kg for colorectal adenocarcinoma), will form a population (originally enrolled part II cohorts) . Also, a pooled population of Part I subjects (n=30) and Part II originally enrolled subjects (n=120) will be used for survival endpoints. The total number of subjects in this dataset is n=148 as there were 2 part I subjects (colorectal adenocarcinoma 0.3 mg/kg) included in Part II.

In the statistical analyses a p-value less than 0.05 will be considered as an indication of statistical significance. If not stated otherwise, all tests will be performed as two-sided tests and two-sided 95% confidence intervals will be produced. Missing values will not be imputed in the analyses.

9.1 Handling of dropouts or missing data

Missing values will not be imputed.

9.2 Interim analyses and data monitoring

The study has 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.

Currently, the study data has been presented for Part I (n=30, reported under separate SAP), and for the Part II population of fully enrolled cohorts (in August 2021 for ESMO and ASCO congresses, all other disease group cohorts than anaplastic thyroid cancer, n=110). Also, a pooled population of Part I and these Part II fully enrolled cohorts (n=138, as there were 2 part I colorectal adenocarcinoma 0.3 mg/kg subjects included in Part II) was used in these presentations.

9.3 Examination of subgroups

All analyses will be presented by tumor type cohorts. In addition, within colorectal adenocarcinoma, results will be presented by dose and by dosing frequency. Furthermore, some disease group cohorts can be combined for subgroup analyses:

- disease cohorts in which there are subjects who have at least SD for overall response evaluation
- cutaneous melanoma, cholangiocarcinoma, gastric adenocarcinoma and hepatocellular cancer which have subjects with a long duration of disease control
- cutaneous melanoma, cholangiocarcinoma and gastric adenocarcinoma cohorts (30 subjects) will be used as a subgroup of investigating the possible predictive markers of clinical benefit, in addition to whole subject population

Subgroup presentations to be done will be indicated in the sections below.

10 Demographic and other baseline characteristics

Number of subjects enrolled into the study at screening and the reasons for screening failures will be summarized. The number of subjects entering and completing the study will be summarized. All subjects discontinuing the study will be summarized together with the reason(s) for discontinuation and time of discontinuation (visit/cycle).

Demographic and baseline characteristics will be summarized by disease group using descriptive statistics. Following variables will be analysed.

- Gender
- Age at entry
- Race
- Weight
- Pregnancy test (females of child-bearing potential)
- Tumour information and other baseline disease characteristics

Medical history, prior and concomitant medications/therapies will be presented by frequency and subject count-based tables according to MedDRA/WHO Anatomical Therapeutic Chemical (ATC) classification.

A prior medication is a medication with end date strictly before administration of first dose of IMP.

11 Extent of exposure and compliance

Treatment exposure (number of cycles), study duration and treatment compliance will be summarised for all subjects and by disease group cohorts using descriptive statistics.

12 Outcome variables

12.1 Primary outcome variables

ORR (CR or PR), CBR (CR, PR or SD) and irORR (irCR or irPR) will be reported as the proportion of subjects of all efficacy evaluable subjects within each tumour type cohort and dosing regimen, both at cycle 4 and at cycle 7. The 90% confidence intervals for ORR, CBR and irORR will be calculated. Results from each tumour type (disease group) will be reported separately. There has been

recent debate about the definition of CBR and DCR. Recent article ("Clinical endpoints in oncology - a primer" by Delgado and Guddati) described that for CBR the SD should last at least 6 months. For clarity, and in order to comply with study protocol the tumour imaging results according the RECIST 1.1 will be presented by cycles (doing so there is no difference in the definition of DCR and CBR). Additionally, we are reporting the duration of SD to capture also that utility.

It should be noted that although the protocol states that irORR should be evaluated, it requires confirmation of irCR or irPR from an additional tumour evaluation carried out at least 4 weeks after irCR or irPR was established. However, due practical limitations in the population of subjects recruited for this study, the additional tumour evaluation could not be carried out on several occasions (only single PR result so far) and for this reason, ancillary information (e.g., no signs of clinical progression) will be reported for patients who continue treatment beyond PD.

When progression occurs, patients can continue treatment if IMP still is judged beneficial for the patient, i.e., clinical status does not indicate progression. This will be summarized using the following categories:

- No evidence of progression
- Evidence of progression, IMP still beneficial
- Evidence of progression, patient withdrawn

This presentation will be done for the first tumor imaging and first time of progression for the DCR subjects. Also, the confirmation image result will be reported for patients continuing IMP beyond progression.

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. The expansion of each disease group cohort is based on CBR (at cycle 4 or at cycle 7 for the Q3W dosing regimen) and the required proportion to proceed to Part III is 1/10. The same definition, CBR at cycle 4 or at cycle 7, will be used for the classification of subjects (DCR vs non-DCR) in the analyses.

12.2 Secondary outcome variables

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. Planned analytes for this are:

- Clever-1 anti-FP-1305 MFI
- Clever-1 anti-9-11 MFI
- Clever-1 anti-FP-1305 % of cells
- Clever-1 anti-9-11 % of cells
- CyTOF
- Response to LPS
- Anti-PD-1 MFI
- Anti-CTLA-4 MFI

S-CLEVER-1: S-CLEVER-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.

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.

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.

12.3 Exploratory outcome variables

The proportion of lymphocyte subsets (CD4, CD8, their ratio, NK-cells, B-cells and regulatory T-cells from CD127 FoxP3 assay) 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 IFN α, IFNγ, IL-1 α, IL-1 β, 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 α, TNF β, GM-CSF, Eotaxin/CCL11, GRO alpha/CXCL1, IP-10/CXCL10, MCP-1/CCL2, MIP-1 α /CCL3, MIP-1 β /CCL4, RANTES/CCL5, SDF-1 α /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.

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 adenocarcinoma 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 immune cell profile, the level of circulating cytokines and chemokines, CLEVER-1 on circulating monocytes, IHC parameters (CD4 positive cells, CD8 positive cells, CD163 positive cells and FoxP3 positive cells) , Clever-1 and PD-L1 staining parameters (intra-tumoral VCs/Positive viable cells/Combined positive score for STAB1, and Combined positive score for PD-L1) and possible genetic analyses during the first four cycles of treatment will be reported using descriptive statistics (by DCR and non-DCR, and in total) and visualizations. If feasible, exploratory statistical analyses will also be used to describe the associations.

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 analyzed 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 tumor type cohort and will be analyzed using the Kaplan-Meier method and Cox-modelling where appropriate.

Duration of response (CR, PR or SD) will be reported using descriptive statistics.

The association of tumor responses to survival will be explored by analyzing the overall survival based on the RECIST outcome at cycle 4 and cycle 7 (disease control subjects vs progressive disease subjects). This analysis will be done using a landmark analysis approach; thus the survival will be calculated from the planned tumor measurement time (cycle 4) and only those subjects who have not discontinued before this landmark time point will be included in this analysis. Also, the effect of the length of latest prior treatment line for the cancer to survival will be explored.

The length of latest prior treatment line will be also compared to length of treatment in this study, and summarized using descriptive statistics as a ratio.

13 PK variables

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 (C_{max}), trough concentration (C_{min}), area under the serum concentration versus time curve (AUC), clearance, volume of distribution, and terminal halflife ($t_{1/2}$) for each dose level will be determined using noncompartmental analysis (NCA). PK parameters will be estimated using version 8.3 of Phoenix® WinNonlin® software (Certara USA, Inc., Princeton, NJ). Results will be presented using descriptive statistics by cycle and each tumour type will be reported separately.

Descriptive statistics for the concentrations by time will be presented using planned timepoints and imputing zero for values below lower level of quantification (LLOQ). NCA calculations will use actual timepoints applying the following rules:

- Actual time of the planned 0 h sample will be set to 0 h and actual times for other samples will be calculated relative to that
- LLOQ concentration values will be set missing

Phoenix® WinNonlin® will use the following settings to compute parameters:

- Linear trapezoidal linear interpolation calculation method
- Uniform weighting
- IV infusion dose
- Plasma model type
- Lambda Z Acceptance Criteria
    - Rsq_adjusted ≥ 0.85
    - Span ≥ 3.0 half-lives
    - Includes ≥ 3 timepoints after Tmax

Selection of points used in the slope parameter calculations will be confirmed visually and may be adjusted if automatic selection of points is seen questionable.

14 Analysis of safety and tolerability

All subjects in the FAS-S analysis set (all subjects receiving study treatment) will be included in the safety and tolerability analysis.

14.1 Adverse events

All recorded adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent adverse event (TEAE) is defined as an AE that begins or worsens in severity after at least one dose of study drug has been administered. Non-treatment emergent AEs are listed only.

TEAEs will be summarized using frequency and subject count tables. TEAEs will be tabulated by disease group, system organ class (SOC), preferred term (PT), causality and severity. For analysis purposes, each subject will also be categorized by the maximum severity reported for a given TEAE (similar PT) and these will be tabulated by maximum severity. If feasible, the AEs will be summarised by treatment cycles.

Serious adverse events (SAEs) and AEs leading to discontinuation will be summarized by disease group.

Pooled AE data from Part I and Part II will be tabulated by dose. Immune-mediated TEAEs will be listed. AE of special interest (AESI) will be listed.

14.2 Laboratory safety variables

Laboratory safety variables comprise of hematology and chemistry parameters. Descriptive statistics will be provided by time point and disease group. Change from baseline (absolute and percentage) will be included in the reporting. Visual illustrations (by subject and by disease group) will be provided. In addition, shift tables (within, below and above the normal range) will be provided for each parameter in relation to the maximum change from baseline from D0 over the complete follow-up period. Some of the laboratory safety parameters can be used also as part of the biomarker analysis.

14.3 Other safety variables

Other safety variable to be analysed are vital signs (body temperature, blood pressure, heart rate), ECG and physical examination.

Absolute values and changes from baseline are both summarized. In addition, the maximum change from baseline over the follow-up period will be calculated for each subject and summarized. Vital signs will be summarized by time point and disease group in terms of mean, median, standard deviation, minimum and maximum.

Physical examination covering all the major organ systems will be performed at screening and pre-treatment within each cycle. These will be summarized by disease groups and visits using frequency and percentage of normal/abnormal observations. Also, ECG evaluation will be summarized using frequency and percentage of normal/abnormal observations

15 Completion and premature discontinuation

Completion and premature discontinuation will be listed. The reasons for premature discontinuation will be presented.

16 Deviations from the analyses planned in the study protocol

There are no major deviations in the SAP from the analyses planned in the study protocol. The analyses defined in this SAP are exploratory. However, since the study still is ongoing certain data is not available yet, e.g., data transfers from laboratories. For this reason, the reporting will not be complete.

The macrophage HLA expression and myeloid derived suppressor cell populations in circulation parameters were not available at the time of execution of this SAP.

17 Execution of statistical analyses

Statistical analyses will be performed by 4Pharma Ltd.

18 Hardware and software

Statistical analysis, tables and subject data listings will be performed with SAS® version 9.4 or later for Windows (SAS Institute Inc., Cary, NC, USA). R may be used for part of the graphical analyses.

19 References

Clinical Study Protocol (FP2CLI001), Final Protocol version 11 (22 December 2021, Faron Pharmaceuticals Ltd.

MATINS Study Protocol Addendum to Investigate the Q2W and Q1W Dosing, version 04 (22 December 2021), Faron Pharmaceuticals Ltd.

MATINS trial Protocol Amendment 08, version 04 (22 December 2021), Faron Pharmaceuticals Ltd.

"Clinical endpoints in oncology - a primer" by Delgado and Guddati, Am J Cancer Res. 2021; 11(4): 1121–1131

20 Appendices

20.1 Table and figure plan

List of planned tables:

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Medical history
Prior medications
Concomitant medications - other than chemotherapy or concomitant procedures
Concomitant medications related to chemotherapy or concomitant procedures
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Overall summary of pooled (Part 1 and Part 2) TEAEs by dose
Section 14.3.3
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Hematology shift
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Regulatory T-cells
Macrophage HLA expression
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Level of circulating cytokines and chemokines by DCR status and overall
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Genetic analyses
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Progression free survival (Kaplan-Meier)

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