OBI Pharma, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL OBI-888-001

A Phase I/II, Open-Label, Dose Escalation and Cohort Expansion Study Evaluating the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Therapeutic Activity of OBI-888 in Patients With Locally Advanced or Metastatic Solid Tumors

Protocol code:	OBI-888-001
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Author:	[redacted]

1. DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date	Author
1.0	31-AUG-2021	[redacted]
2.0	02-JUN-2022	[redacted]

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
2.0	Throughout the document	Editorial changes and updates to reflect an abbreviated CSR (aCSR).	After 01Dec2021 Sponsor elected to generate an aCSR focusing on safety and exposure.
	3.0	Sentence added about aCSR.	To clarify the scope of the TFLs that will be generated.
	5.3	Section on Data Safety Monitoring Board renamed to Safety Review Committee (SRC) and details on SRC responsibilities added.	Text added to reflect the protocol.
	8.0	Sentence “Exploratory analyses will be conducted by OBI Translational Biology (or their designee) and may be included in the aCSR.” added.	To clarify responsibilities.
	8.0 - 8.3	Added asterisks to show which endpoints will be analyzed	The aCSR will not include all endpoints planned in the protocol.
	9.0, 10.7	Update analysis populations.	Since safety is now the main focus of the analysis, the analysis populations will be limited to safety and PK

Version #	Chapter	Revision Summary	Reason(s) for Revision
			populations.
	10.2	Sentence “Per protocol, assessments performed at Day 1 should be obtained prior to infusion of the study drug. As only dates (without time) of assessments are recorded, the last assessment with date prior or same as the first dose date will be considered baseline.” Added.	To clarify selection of baseline assessment.
	10.3, 10.7.2	Removal of ORR, DOR and PFS endpoints.	ORR, PFS and DOR analyses will no longer be conducted.
	10.4, 10.5, 10.6, 10.6.2, 10.7.1, 10.7.2, 10.8.2, 10.8.3, 10.8.4, 10.8.5	Remove description of summary tables.	Analyses removed to support aCSR which focuses on safety and exposure.
	10.6.1	Summary for Globo-H score at baseline added.	To reflect mock-up TFLs table 14.1.2.1 content.
	10.6.1	Weight at screening changed to weight at baseline.	To correctly describe baseline characteristics that will be summarized.
	10.6.2	Time since initial diagnosis (months) and tumor size at first diagnosis (mm) added.	Added to provide better presentation of patients’ baseline characteristics.
	10.6.2	Cancer type for Part A removed.	To reflect data collected in the eCRF.
	10.6.3	Subsection “Other Patient Characteristics” added.	To clarify patient characteristics that will be summarized only in listings.
	10.7.1	Dose limiting toxicities (DLTs) categories modified.	To reflect data collected on eCRF.
	10.7.1	Added asterisks to show which adverse events will be analyzed.	The aCSR will not include all adverse events planned in the SAP v1.0.

Version #	Chapter	Revision Summary	Reason(s) for Revision
	10.7.1	Treatment emergent adverse event (TEAE) definition added. NCI CTCAE version changed from 5.0 to 4.03. Relationship to study drug terms modified. Description of TEAE listing leading to study drug discontinuation modified, information on reporting to which drug(s) has been discontinued removed.	To follow protocol terminology.
	10.7.1	Added TEAEs leading to death to list of tables that will be produced	Correction of omission.
	10.7.1	Following paragraphs removed: AEs will be summarized by study part, dose, cohort, system organ class (SOC), preferred term (PT), severity grade, and relationship to treatment. SAEs, deaths, and AEs leading to early treatment discontinuation (collected on Adverse Events eCRF page) will be summarized. All the dose escalation incidences of AEs, SAEs, abnormal laboratory parameters, clinically significant laboratory abnormalities, and vital signs will be reported as well.	Not to repeat information which is provided in detail in the same section.
	10.7.1	Instead of producing a listing with DLTs, DLT flag is included in the listing with all AEs.	To clarify which listings are produced.
	10.7.1	Listing with AEs grade ≥ 3 added.	Correction of omission.
	10.7.2	Definition of CBR modified: confirmed complete response (CR) and confirmed partial response (PR) should be used.	Text added to follow the protocol.

Version #	Chapter	Revision Summary	Reason(s) for Revision
	10.7.2	Sentence “PK and PD analyses will be performed by OBI Pharma, Inc.” added.	To clarify the responsibilities.
	10.8.1	Units corrected for actual dose received from mg/kg to mg.	To reflect units collected on eCRF.
	10.8.1	Repeated analyses removed.	For consistency.
	10.8.1	Number of total doses received added.	To reflect mock-up TFL table 14.3.1.1 content.
	10.8.2	“No CTCAE grade” changed to “grade 0”.	For consistency with mock-up TFL table 14.3.12.1.1.
	10.8.2	Summary for worst-post baseline NCI CTC grade for applicable laboratory tests added.	Added to provide better presentation of laboratory results.
	10.8.2	Pregnancy results will be listed.	To clarify what laboratory data will be listed.
	10.8.3	Changes from baseline for vital signs added.	To reflect mock-up TFL table 14.3.14.1-2 content.
	20	Programming specification section removed	Not to repeat information which is included in Mock-Up Tables, Figures and Listings document.

APPROVAL SIGNATURES

STUDY TITLE: A Phase I/II, Open-Label, Dose Escalation and Cohort Expansion Study Evaluating the Safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and Therapeutic Activity of OBI-888 in Patients with Locally Advanced or Metastatic Solid Tumors

PROTOCOL NUMBER: OBI-888-001(V 5.0, 08-May-2020)

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TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
aCSR	abbreviated Clinical Study Report
ADAs	anti-drug antibodies
ADCC	antibody-dependent cell mediated cytotoxicity
AE	adverse event
BMI	body mass index
BOR	best overall response
C	cycle
CBR	clinical benefit rate
CDC	complement dependent cytotoxicity
CI	Confidence interval
CR	complete response
CT	computed tomography
D	day
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FFPE	formalin fixed paraffin embedded
HLA	human leukocyte antigen
IHC	immunohistochemistry
IV	intravenous(ly)
KIR	killer cell immunoglobulin-like receptor
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NE	non-evaluable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	objective response rate
PD	pharmacodynamics
PD-L1	programmed death – ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors

RP2D	recommended phase II dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System organ class
SRC	Safety review committee
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocytes

3. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol OBI-888-001 final version 5.0 (dated 08 May 2020), and electronic case report form (eCRF) production version 5.4 dated 17 Nov 2020.

The Sponsor elected to generate an abbreviated Clinical Study Report (aCSR) focusing on safety and exposure.

4. STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVES

The primary objectives are:

- To evaluate the safety and tolerability of OBI-888 when administered intravenously (IV) to patients with locally advanced or metastatic solid tumors.
- To determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of OBI-888 as monotherapy.

4.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the preliminary clinical activity profile (objective response rate [ORR], clinical benefit rate [CBR], duration of response [DOR], and progression-free survival [PFS]) of OBI-888.
- To evaluate the immunogenicity of OBI-888 (anti-drug antibodies [ADAs]).
- To determine the serum pharmacokinetics (PK) and pharmacodynamics (PD) of OBI-888.

4.3 EXPLORATORY OBJECTIVES

Exploratory objectives are:

- To assess antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC).
- To identify potential predictive biomarkers.
- To assess the expression of immune markers including immune checkpoints, in the tumor tissue samples.
- To assess the expression of Globo H and related tumor-associated glycans in the tumor tissue.
- To perform glycan analysis of OBI-888.

5. STUDY DESCRIPTION

5.1 STUDY DESIGN

This is a Phase I/II, open-label, dose escalation and cohort expansion study of OBI-888, a humanized monoclonal antibody (mAb) targeting Globo H, in patients with locally advanced or metastatic solid tumors.

This is a 2-part study. Part A (Dose Escalation) is designed to establish the MTD and RP2D of OBI-888. Part B (Cohort Expansion) is intended to further characterize the safety and clinical activity profile of the RP2D dose of OBI-888 administered as monotherapy in patients with locally advanced or metastatic solid tumors.

5.1.1 PART A-DOSE ESCALATION

The dose escalation part of the study included 3 cohorts of escalating dose levels of 5, 10, and 20 mg/kg, using 3+3 design to identify MTD and RP2D.

Three patients were enrolled at the lowest dose level. If none of the 3 patients experienced a dose-limiting toxicity (DLT), the next cohort of 3 patients were to be enrolled at the next higher dose level. If 1 of 3 patients in the initial dose cohort experienced a DLT, that cohort was expanded to 6 patients. If only 1 of these 6 patients had a DLT, then the next cohort of 3 patients were enrolled at the next higher dose level. If 2 or more patients of the 3-6 patients in a cohort experienced a DLT, dose escalation ceased and that dose level was above the MTD (the highest dose where no more than 1 of 6 patients had experienced at DLT). New patients were enrolled at the previous lower (tolerated) dose level until that cohort had 6 patients. This lower dose level was to be considered the MTD if ≤ 1 in 6 patients had a DLT.

Patients should receive all four planned doses with OBI-888 administered during Cycle 1 to be eligible for DLT evaluation, unless they experienced a DLT with any dose. A patient who withdrew from the study within the DLT evaluation period for reasons other than drug-related adverse event (AE) was not included for DLT evaluation and was to be replaced; but could continue to receive study treatment after slipped dose, if still eligible for treatment.

Escalation to higher OBI-888 dose cohort was not permissible during the study. After a DLT was experienced by patients, dose interruptions, modifications or dose delays may have applied, as per Investigators' judgement (refer protocol section 8.3).

5.1.2 PART B-COHORT EXPANSION

At the time of this version of the SAP, Part A (Dose Escalation) was completed. No DLTs were observed at any dose level tested in Part A, and the MTD was not reached. Therefore, dosing in Part B was initiated at the highest dose tested in Part A (20 mg/kg OBI-888).

Part B was planned to enroll a maximum of 150 additional patients with advanced solid tumors with high Globo H expression (defined as an H-score cutoff ≥ 100 using a validated immunohistochemistry [IHC] assay) across 4 disease-specific cohorts and 1 basket cohort based on a Simon two-stage design. The first stage of Part B recruited up to 9 patients in each cohort (up to 45 patients in the first stage across all cohorts). If sufficient evidence of activity was observed in the first stage, up to 21 additional patients were to be enrolled into that cohort (up to 105 patients in the second stage across all cohorts).

Part B was conducted to obtain additional safety data, characterize the PK and PD profiles of OBI-888, obtain a preliminary assessment of the clinical activity of OBI-888 in Globo H expressing solid tumors, and inform subsequent efficacy-finding clinical development.

The following 5 cohorts of patients who had high expression of Globo H by a qualified laboratory assessment (i.e., Globo H H-score ≥ 100 using a validated IHC assay) were to be enrolled in Part B.

Cohort 1: Pancreatic cancer

Cohort 2: Esophageal cancer

Cohort 3: Gastric cancer

Cohort 4: Colorectal cancer

Cohort 5: Basket (any solid tumor type other than those included in Cohorts 1 through 4)

All patients were required to provide a tumor biopsy sample, either unstained slides (preferred) or a formalin fixed paraffin embedded (FFPE) tissue block at the initiation of screening visit for screening for Globo H overexpression and confirmation for eligibility of patients for Part B. Patients with a confirmed and documented Globo H H-score of ≥ 100 were eligible for the study and were subsequently entered into the 28-day screening period to complete the remaining screening procedures.

Patients were to continue to receive treatment with OBI-888 until progressive disease, unacceptable toxicity, or a decision by the Investigator or patient to discontinue treatment.

5.2 STUDY TREATMENT

OBI-888 was administered as an IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle in Part A and Part B of the study.

For Part A (Dose Escalation), OBI-888 was given at doses of 5 mg/kg, 10 mg/kg and 20 mg/kg to the 3 dose cohorts.

For Part B (Cohort Expansion), patients were to be treated with 20 mg/kg OBI-888 since no DLTs were observed at any dose level tested in Part A, and the MTD was not reached.

Treatment was to continue until progressive disease, unacceptable toxicity, or a decision by the Investigator or patient to discontinue treatment.

OBI-888 investigational drug solution (OBI-888 drug product mixed with saline/glucose infusion solution) was to be administered as an IV infusion by the site staff.

The infusion was to be given for a duration of approximately 90-minutes (±10 minutes), for the initial two cycles (C1 and C2).

The infusion duration from Cycle 3 could be reduced, if no infusion related AEs to prior infusions occurred, to 30 minutes or 60 minutes at the discretion of the Investigator.

5.3 SAFETY REVIEW COMMITTEE

The Safety Review Committee (SRC) for OBI-888-001 study consisted of the clinical lead, medical monitor, and the study Investigator(s) or designee. The SRC was to act in an advisory capacity to monitor patient safety and efficacy during the trial.

This Committee was to convene after each cohort completed the first cycle of treatment during the dose escalation phase, to review safety data (AEs and laboratory toxicities) to determine whether DLTs occurred. Based on DLTs in Part A with consideration of available PK and PD data, RP2D for Part B (Cohort Expansion) was to be recommended by SRC. The SRC was to convene at regular intervals during the conduct of the Cohort Expansion portion of the study to assess safety and activity.

6. RANDOMIZATION AND BLINDING

The study is a Phase I/II, open-label, dose escalation and cohort expansion study and did not involve randomization; patients and members of the clinical study team were not to be blinded to treatment.

7. SAMPLE SIZE AND POWER CALCULATION

This was a 2-part study: Part A Dose Escalation and Part B Cohort Expansion.

14 patients enrolled in the 3+3 dose escalation phase (Part A).

The cohort expansion phase (Part B) was to enroll up to 150 total patients based on a Simon two-stage design. The first stage was to recruit up to 9 patients in each cohort. If at least 1 objective response was observed within the first 6 cycles of therapy, a second stage recruitment was to occur with up to 21 additional patients enrolled into that cohort, for a total of up to 30 patients per cohort. If at least 4 objective responses were observed within the first 6 cycles of therapy in 30 patients, then OBI-888 was considered worthy of further evaluation in that indication. This design is based on a level of low interest for a treatment with an ORR of 5% versus a level of high interest for a treatment with an ORR of 25%. The sample size was based on a one-sided alpha of 0.05 and 90% power. The two-stage design limits the number of patients treated for a treatment with low levels of activity.

8. ANALYSIS ENDPOINTS

Analysis endpoints are listed as per protocol. Only those endpoints marked with * will be analyzed in the aCSR. Exploratory analyses are to be conducted by OBI Translational Biology (or their designee) and may be included as appendices in the aCSR.

8.1 PRIMARY ENDPOINTS:

- DLTs with OBI-888*.
- AEs/ serious AEs (SAEs) and laboratory abnormalities as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03*.
- MTD and RP2D of OBI-888.

8.2 SECONDARY ENDPOINTS:

- Percentage of patients with ORR, CBR*, DOR and PFS according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).
- Percentage of patients with anti-OBI-888 ADAs in blood*.
- PK and PD parameters of OBI-888*.

8.3 EXPLORATORY ENDPOINTS:

- Globo H and related glycan expression in tumor tissue by IHC.
- ADCC and CDC.
- Identify potential predictive markers by IHC or molecular analysis.
- Tumor Infiltrating Lymphocytes (TILs) including natural killer (NK) cells, and programmed death – ligand 1 (PD-L1) expression in tumor tissue samples by IHC.
- Killer cell immunoglobulin-like receptor (KIR), human leukocyte antigen (HLA), and Fc receptor gamma genotype.
- Glycan analysis of OBI-888.

9. ANALYSIS POPULATIONS

Safety population: all enrolled patients who received at least 1 dose of study drug. This analysis set will be used for all endpoints and analyses except PK.

PK population: all enrolled patients who received at least 1 dose of study drug and had sufficient PK samples (a sample at the end of administration and at least 3 samples during the elimination phase) will be included in the PK assessments. This analysis set will be used for all PK endpoints.

10. ANALYTICAL PLAN AND STATISTICAL METHODS

10.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be conducted and data appendices will be created using the SAS system version 9.4 or higher.

Data collected in this study will be presented in patient data listings and summary tables.

Descriptive statistics (number of patients with non-missing values, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. All raw data will be presented to the original number of decimal places. Means and medians will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data.

Frequency distributions (counts and percentages) will be presented for categorical variables. Discrete variables that are ordinal-scaled (e.g., ECOG performance score) will additionally be presented with mean scores and standard deviations. If not specified otherwise, the number of observations with non-missing values will be the denominator for percentage calculation. Further details on the handling of missing observations are presented in section 10.3.

If days are converted to months, a factor of 30.4 days/month will be used. If days are converted to years, a factor of 365.25 days/year will be used. Time will be shown in study weeks, i.e. number of weeks from the first administration of any study drug.

Dose escalation (Part A). The dose-escalation analysis will be presented by OBI-888 dose (5 mg/kg, 10 mg/kg or 20 mg/kg) cohorts and overall. The following cohorts and overall will be presented:

- OBI-888 5 mg/kg
- OBI-888 10 mg/kg
- OBI-888 20 mg/kg
- Dose Escalation Total

Expansion cohorts (Part B). The expansion part analysis will be presented by cancer diagnosis. The following cohorts and overall will be presented:

- Cohort 1: Pancreatic cancer
- Cohort 2: Esophageal cancer
- Cohort 3: Gastric cancer
- Cohort 4: Colorectal cancer
- Cohort 5: Basket (any solid tumor type other than those included in Cohorts 1 through 4)

- Cohort Expansion Total

10.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Baseline for each assessment is defined as the result of the last assessment prior to first dose of study drug. Per protocol, assessments performed at Day 1 should be obtained prior to infusion of the study drug. As only dates (without time) of assessments are recorded, the last assessment with a date prior to or the same as the first dose date will be considered baseline.

The data will be analyzed according to the visits recorded in the eCRF. No additional visit windows will be applied. In listings, any unscheduled visits will be inserted in the appropriate temporal sequence using visit date and time.

10.3 HANDLING OF MISSING DATA

For the calculation of the time since initial cancer diagnosis, the following imputation rules will be applied when the date of initial cancer diagnosis is incomplete:

- If the day is missing: first day of the month.
- If the day and month are missing: first day of January.

Partial or missing start and end dates of AEs and concomitant medications will be imputed conservatively based on the rule described in Appendix II: Imputation rules for missing dates. The imputed dates will be used to allocate the AEs and concomitant medications to a study period, and to determine whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

For CBR endpoint, patients with missing data (for any reason) will be included as non-responder.

10.4 PATIENT DISPOSITION

Patients in each analysis population, as well as patients who complete the treatment, complete the study, and patients who prematurely discontinue from treatment and from the study, together the with number of enrolled patients will be tabulated as indicated in section 10.1. The number and percentage within each category will be presented.

The number and percentage of patients included in the safety and PK populations will also be summarized by study part, and cohort (and for Phase B).

A listing with all enrolled patients will be generated for the study to describe country/study center, patient number, study part, cohort, first and last study drug dosing dates, total duration of study drug dosing, the reason for discontinuing study drug dosing, end of study date, and reason for discontinuing the study.

10.5 PROTOCOL DEVIATIONS

Protocol deviations and their classification (minor/major) will not be summarized.

Protocol deviations will be classified as major and minor as specified in the Protocol Deviations Management Plan. Patients with major protocol deviation will be identified and documented before the database lock.

10.6 PATIENT CHARACTERISTICS

Patient characteristics will be summarized for safety population.

10.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Descriptive statistics for continuous variables (age at screening, height, weight at baseline, and BMI [body mass index]) and frequency counts and percentages for categorical demographic variables (gender, ethnicity, race, Globo-H score, and Eastern Cooperative Oncology Group [ECOG]) performance will be summarized by study part, and cohort using the safety population.

BMI will be derived as: BMI [kg/m^2] =weight[kg]/(height[cm]/100)^2.

Height reported in inches will be converted to centimeters as: height [cm] = height [in] * 2.54.

Demographic and baseline characteristics will be provided in a listing.

10.6.2 CANCER DIAGNOSIS HISTORY

Part A

Time since initial diagnosis (months), tumor size at first diagnosis (mm), tumor type and location, TNM stage of disease at diagnosis and at study entry, presence and location of metastasis, most recent treatment prior to screening, TNM classification at study entry will be tabulated. Descriptive statistics will be used to describe tumor size at first diagnosis. Data will be summarized in the safety population by dose and overall.

Colorectal cancer history, pancreatic cancer history, and gastric/gastroesophageal junction or esophageal cancers history will not be summarized separately.

Part B

In patients who have cancer history to be reported, stage of disease at diagnosis, time since initial diagnosis (months), metastasis (yes/no), and sites of metastases (liver, peritoneum, lung, bone, regional lymph nodes, other) will be tabulated. Descriptive statistics will be used to describe the number metastases' sites.

Cancer diagnosis history will be listed.

10.6.3 OTHER PATIENT CHARACTERISTICS

Following patient characteristics will be listed:

- Medical history and current medical conditions
- Prior and concomitant medications
- Prior anticancer therapy
- Smoking history

10.7 ANALYSIS OF STUDY ENDPOINTS

This section describes analysis of primary, secondary and exploratory endpoints. All endpoints will be analyzed using planned treatments. Summaries will be presented for safety population.

10.7.1 PRIMARY ENDPOINTS

A. DLTs with OBI-888

The period for DLT is 28 days from the start of first dose of Investigational Product at Day 1 in study part A.

A DLT is defined as the occurrence of any of the following events within the first cycle of treatment and are considered to be at least possibly related to OBI-888:

- Grade 4 neutropenia
- Grade ≥ 3 febrile neutropenia with or without infection
- Grade 4 thrombocytopenia
- Grade ≥ 3 nausea and vomiting or diarrhea for more than 72 hours despite optimal supportive care
- Any Grade ≥ 3 non-hematological AE, except for nausea, vomiting, or diarrhea that does not resolve before the next infusion
- Grade 4 infusion reactions, and Grade ≥ 3 infusion reactions that recur despite decreasing infusion rate and optimal supportive care measures

DLTs will be displayed by assigned dose and cohort in a frequency table in decreasing order of incidence. DLTs will not be programmatically derived but analyzed as collected on the eCRF.

AE terms will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be graded according to the NCI CTCAE version 4.03. All AEs unless they have been determined to be not related to study drug will be taken into consideration in determining DLTs.

B. AEs/SAEs and laboratory abnormalities as graded by NCI CTCAE version 4.03

A treatment-emergent adverse event (TEAE) is defined as an AE with onset dates on or after the start of study drug or if it is present prior to receipt of the study treatment but worsens in severity or increases in frequency on or after the first dose. AEs having both onset and end dates missing will be considered as TEAEs.

Events reported as “Unrelated” or “Unlikely related” to study drug will be considered as unrelated to the study drug. Events reported as “Possibly related”, “Probably related”, “Definitely related” to study drug or without relationship information will be considered as related to the treatment.

Tables will display the incidence of events (number of events, number of patients with any event, number of patients with any event in each specific system organ class [SOC], and number of patients with any event for each specific preferred term [PT]).

For each AE, only the highest grade and closest association with study drug by patient will be considered in the incidence analyses.

The following tables will be produced:

Tables by SOC and PT will be displayed for following AEs. Only those AEs marked with * will be

analyzed in the aCSR:

- DLTs
- Treatment-emergent adverse events (TEAEs)*
- TEAEs grade ≥ 3*
- TEAEs related to OBI-888*
- TEAEs leading to discontinuation of OBI-888*
- Serious TEAEs
- Serious TEAEs related to OBI-888*
- AEs leading to discontinuation of OBI-888
- SAEs leading to discontinuation of OBI-888
- TEAEs leading to death*

A table of TEAEs by SOC, PT and worst CTCAE grade (per summarization level) will be presented.

The following listings will be prepared:

- All AEs, with DLTs flagged
- All SAEs
- AEs related to OBI-888
- AEs grade ≥ 3
- All TEAEs leading to OBI-888 discontinuation
- AEs leading to death

C. MTD and RP2D of OBI-888

The MTD and RP2D were identified as 20 mg/kg during SRC review.

10.7.2 SECONDARY ENDPOINTS

A. Percentage of patients with CBR according to RECIST 1.1

CBR: Defined as the proportion of patients with confirmed complete response (CR), partial response (PR) or stable disease (SD) among all the treated patients (including non-evaluable [NE] ones). A confirmed response will be defined as two or more consecutive assessments separated by at least 3 weeks. The 95% confidence interval (CI) will be estimated using the exact binomial distribution. The CBR summary table will be supported by the overall tumor response listing.

If an NE response is determined at a time point, this response will be ignored and subsequent non-NE response will be used for the confirmation. For example, the sequence of tumor assessments: PR, NE, NE, CR, SD, that had more than one consecutive NE, the third subsequent non-NE response (CR) is used as the confirmation of the first PR for best overall response derivation.

A requirement for SD is that it should be met at least once ≥ 6 weeks after the first dose of trial treatment, otherwise the best response will be NE.

The criterion for confirmation of the response is summarized in the following table (Eisenhauer et al, 2009):

Overall response first time point	Overall response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR [1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

[1] If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have re-appeared after CR). Best response would depend on whether minimum duration of SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to a PR and the best response is PR.

Overall tumor response (not to be programmatically derived and collected on eCRF) will be listed by assigned dose, cohort, and visit.

B. Percentage of patients with ADAs in blood

The number and percentage of patients with positive ADAs in the blood will be summarized for the safety population.

C. PK and PD parameters of OBI-888

Pharmacokinetic Analysis

PK and PD analyses will be conducted by OBI Pharma, Inc. Please refer to statistical analysis plan developed for PK and PD parameters (Appendix III).

10.7.3 EXPLORATORY ENDPOINTS

- Globo H and related glycan expression in tumor tissue by IHC
- ADCC and CDC
- Identify potential predictive markers by IHC or molecular analysis
- TILs, including NK cells, and
  PD-L1 expression in tumor tissue samples by IHC

- KIR, HLA, and Fc receptor gamma genotype
- Glycan analysis of OBI-888

The above analyses will be conducted by OBI Translational Biology (or their designee). Details of these analyses will be provided in separate document(s). The results will be compiled into a separate appendix in Section 14 of the aCSR.

10.8 SAFETY ENDPOINTS

This section describes the safety endpoints that are not part of the primary, secondary, or exploratory endpoints previously described in section 10.7.

All safety endpoints will be analyzed using the safety population based on treatments the patients actually received during the study.

Safety will be evaluated by presenting summaries of exposure to study treatment, laboratory evaluations (hematology, chemistry, coagulation, and urine analysis), vital signs, and other parameters.

10.8.1 EXPOSURE TO STUDY TREATMENT

The number of doses received, actual dose received in mg, the total planned dose in mg/kg and the extent of exposure, (calculated as last dose date - first dose date +1), will be summarized using descriptive statistics by cohort, study part and overall.

A by-patient listing with the treatment administration data will be also presented and reasons for doses missed will be also listed.

10.8.2 LABORATORY DATA

Tables by visit and by NCI CTC grades (grade 0, grade 1, grade 2, grade 3, grade 4, grade 5) will be presented by laboratory test, where applicable. Worst-post baseline NCI CTC grade for applicable laboratory tests will be also summarized.

Urinalysis results (normal/ abnormal – low/ abnormal - high) will be summarized by visit.

Data listings will be produced for all collected laboratory data, including pregnancy test results.

10.8.3 VITAL SIGNS

Vital signs assessments (temperature, pulse, systolic and diastolic blood pressure) and weight will be tabulated by visit (results and changes from baseline).

Data listings will be produced for all collected vital signs data.

10.8.4 ELECTROCARDIOGRAM

Data listings for electrocardiogram (ECG) data will be produced.

10.8.5 OTHER SAFETY PARAMETERS

ECOG will not be summarized.

Physical examination results (normal/abnormal-not clinically significant/abnormal-clinically

significant) will be summarized by visit and listed.

11. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

The Sponsor elected to generate an aCSR focusing on safety and exposure. As a result, the following analyses will not be conducted: DOR, best overall response (BOR), PFS, ORR. Protocol deviations will not be summarized nor listed. Medical history, current medical conditions, prior and concomitant medications, prior anticancer therapy, and smoking history will be summarized in the listings only. Serious TEAEs and SAEs leading to discontinuation of OBI-888 will not be summarized. Shift tables of the worst on study laboratory toxicity based on NCI CTCAE grading will not be presented; summaries of laboratory data (with exception of summary described in section 10.8.2), and ECOG over time will not be presented.

DLT criteria as collected on eCRF will be analysed.

12. LIST OF TABLES, LISTINGS, AND FIGURES

Shells for unique tables, listings and figures are provided in a separate Mock-Up tables, figures, and listings (TFLs) document.

13. REFERENCES

Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors Journal of the National Cancer Institute, Vol. 92, No. 3, February 2, 2000.

14. APPENDIX I. SCHEDULE OF ASSESSMENTS

TABLE 14-1 SCHEDULE OF ASSESSMENTS

Schedule of Assessments

Study Procedure	**Screening Visit****	**Treatment Period**					**EoS / ET**
Cycle (C) #	-	**Cycle 1**				**Cycle 2-13**	
Cycle # and Day		C1D1	C1D8	C1D15	C1D22		
Window period (days)	-28 to -1 days	-1*	±1	±3	±3	±3 days	±7 days
Informed consent[a]	X						
Demographics	X						
Eligibility screening	X	X					
Medical history[b]	X	X					
Physical examination[c]	X	X	X	X	X	X	X
Height, weight[d]	X	X	X	X	X	X	X
Vital signs[e]	X	X	X	X	X	X	X
ECOG[f]	X					C2D1 only	X
12-lead ECG[g]	X	X	X			C2D1 only	X
Pregnancy testing[h]	X						X
Tumor biopsy[i]	X**						
Hematology and Biochemistry [j]	X	X	X	X	X	Every 2 weeks (D1 and D15 of each Cycle)	X
Coagulation and Urinalysis[k]	X	X				Every 2 cycles, D1 (C2 C4, C6, C8, C10, C12)	X
Drug administration[l]		X	X	X	X	D1, D8, D15, D22 of each 28 day cycle	
Pharmacokinetic sample[m]		See footnote m and Table 14-2 (Part A) and Table 14-3 (Part B)					
Immunogenicity (ADA)[n]		See footnote n and Table 14-2 (Part A) and Table 14-3 (Part B)					
Biomarkers[o]	X	See footnote o and Table 14-2 (Part A) and Table 14-3 (Part B)					
Radiology evaluations (CT or MRI)[p]	X					End of every 2 cycles	X
Concomitant medications	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X

EOS/ET - End of Study/Early Termination. EoS Visit is the safety follow-up visit, conducted

28±7 days after the last OBI-888 dose. ET visit lab assessments will be conducted for patients discontinuing study treatment, if last available tests are before 2 weeks.

*The - 1 day window (1 day prior) for C1D1 is for safety laboratory assessments. Blood can be drawn 1 day prior to initiation of study drug infusion on C1D1. Safety laboratory results should be available and reviewed by the Investigator prior to the OBI-888 administration.

** All patients are required to provide a tumor biopsy sample, unstained slides (preferred) or a FFPE tissue block at the initiation of screening visit for screening of Globo H overexpression and confirmation for eligibility of patients for Part B. Patients with a confirmed and documented Globo H H-score of ≥ 100 are eligible for the study, and will subsequently enter the 28-day screening period to complete the remaining screening procedures.

Footnotes:

a. Informed consent to be obtained before any other study procedures are performed.
b. Medical history to include previous cancer therapies, cancer history, and past and ongoing concomitant illnesses.
c. A complete physical examination is required at screening and at discontinuation. Directed physical examinations may be limited to problem focused review of symptoms and major organ systems
d. Height to be obtained at screening only.
e. Vital signs include temperature, blood pressure and pulse (at supine position). Temperature measurement will be obtained as clinically indicated.
f. ECOG performance status: at baseline, C2D1 and end of study/early termination
g. 12-lead ECG: at screening and post infusion at C1D1, C1D8, and C2D1 (within one hour after end of infusion); and end of study/ early termination
h. Pregnancy testing should be performed in females of childbearing potential only. A serum pregnancy test is required during screening. A urine or serum pregnancy test is acceptable end of study or early termination
i. Tumor biopsy samples are mandatory at screening visit. Fresh (preferred) tissue or archival tissue is acceptable. A minimum of 3 slides are required for the central laboratory Globo H assay for determination of eligibility. Up to 12 unstained additional slides should be provided, depending upon availability, for the protocol-defined exploratory studies.
j. Hematology and Serum chemistry (Laboratory Assessments: Protocol Table 12-1). Blood draw is prior to OBI-888 infusion.
   Hematology: hematocrit, hemoglobin, erythrocyte count, white blood count (WBC), absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count. Serum chemistry: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, creatine kinase, LDH, total bilirubin, and uric acid. Creatinine clearance will be calculated by Cockcroft Gault equation at screen visit, week 1 and EOS/early termination.
k. Coagulation, and Urinalysis (Laboratory Assessments: Protocol Table 12-1) Blood draw and urine collection is prior to OBI-888 infusion.
   Coagulation: PT, aPPT, and INR. Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick. A microscopic urinalysis (only if needed) evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals
l. OBI-888 is given in cycles with each individual cycle consisting of 28 days (4-week cycle). IP is administered on weekly basis (within cycle as C1D1, C1D8, C1D15, and

C1D22; C2D1, C2D8, and so on; for a total of 13 cycles, or disease progression or unacceptable toxicity, whichever occurs earlier.

m. Pharmacokinetic: (for analysis of serum concentration of OBI-888). Detailed schedules are provided in Table 13-2 (Part A) and Table 13-3 (Part B).
n. Immunogenicity studies (ADA) - ADA samples will be collected at the same time points, along with pre-infusion only PK samples. No post-infusion ADA samples will be collected. Detailed schedules are provided in Table 13-2 (Part A) and Table 13-3 (Part B). For patients with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.
o. **Biomarker**: Detailed schedules are provided in Table 13-2 (Part A) and Table 13-3 (Part B).
p. Radiology (CT or MRI scan) evaluations of tumor response: Performed during screening and during the study at the end of every second cycle (8 weeks) at: C2, C4, C6, C8, C10 and C12. CT or MRI scan will be performed within 1 week prior to the start of the next cycle. Unscheduled scan can be perform anytime, if needed to confirm disease progression. Radiology assessment for early termination/end of study, should only be performed if 8 or more than 8 weeks (≥8 weeks) have passed from the previous scheduled CT/MRI scan. Same assessment method and same technique should be used on each patient while on study.

TABLE 14-2 PART A – PHARMACOKINETIC, ADA, BIOMARKER, AND GLYCAN SAMPLING SCHEDULE

Cycle (C)	**Cycle 1**						**Cycle 2**		**Every 2 Cycles[e, h]**	**EoS / ET**
Cycle Day	**D1**	**D2**	**D4**	**D8**	**D15**	**D22**	**D1, 8, 15**	**D22**	**D1**	**±7 days**
Pharmacokinetic Samples										
Before infusion	X[a]			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X
End of infusion (90 minutes)[c]	X	X[d]	X[d]	X	X	X	X	X		
1 hour after end of infusion (150 minutes)[e]	X									
4 hours after end of infusion (330 minutes)[e]	X									
8 hours after end of infusion (570 minutes)[e]	X									
Immunogenicity studies (ADA)[f]	X			X	X	X	X	X	X	X
Glycan analysis[g]	X			X	X	X	X	X		
Biomarkers										
ADCC[i]	X				X			X	C4D1	X
CDC/ADCC[i]	X			X	X					
KIR, HLA, Fc receptor gamma genotyping[i]	X									X

ADA = antidrug antibody; ADCC = antibody-dependent cell-mediated cytotoxicity; C = cycle; CDC = complement dependent cytotoxicity; D = day; EoS/ET = End of Study/Early Termination; HLA = human leukocyte antigen; KIR = killer cell immunoglobulin-like receptor

Note: OBI-888 infusion should be administered on Days 1, 8, 15, and 22 of every 28-day cycle throughout the study treatment period.

The infusion duration of Cycle 1 and Cycle 2 are 90 minutes, and can be reduced to 30-60 minutes for Cycle 3, if there were no infusion related adverse events on prior infusions and at the discretion of the investigator.

a. C1D1 Pre-infusion serum samples can be drawn within 1 day prior-to the infusion.

b. Pre-infusion serum samples can be collected at any time prior to the infusion on the day of the infusion.

c. Post infusion samples at the end of infusion and later (at 1, 4, and 8 hours after the end of the infusion) can be collected in a window of ±15 minutes.

d. For Cycle1 Days 2 and 4, a single sample will be collected (window ±2 hours):

- 24 hours after end of infusion (for infusion at C1D1)

- 72 hours after end of infusion (for infusion at C1D1)

e. If there is change of the infusion rate or interruption of infusion, the PK sampling at Day 1 are to be collected from the exact time of completion of infusion to obtain the post-infusion samples at 1, 4, 8 hour at the end of infusion. Exact time of sample collection and the reason for interruption should be documented in the eCRF.

f. ADA sample will be collected along with the pre-infusion PK samples according to the above table. No post-infusion ADA samples including C1D2 and C1D4 will be collected. For patients with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.

g. Glycan analysis: pre-infusion and end of infusion in cycle 1 and 2 only. Residual PK and ADA samples will be pooled for glycan analysis after PK and ADA data are finalized.

h. Samples to be collected on Day 1 of C4, C6, C8, C10, C12.

i. Biomarkers:

- ADCC (effector cell): pre-infusion blood sample will be collected at C1D1, C1D15, C2D22, C4D1 and end of study/early termination.
- CDC/ADCC (humoral): pre infusion and end-of-infusion blood sample will be collected at C1D1, C1D8, and C1D15.
- KIR, HLA, Fc receptor gamma genotyping: blood sample will be collected at C1D1 (pre-infusion) and end of study/early termination.

TABLE 14-3 PART B – PHARMACOKINETIC, ADA, AND BIOMARKER SAMPLING SCHEDULE

Cycle (C)	**Screening**	**Cycle 1**						**Cycle 2**	**Every 2 cycles starting with Cycle 3 [a]**	**Every 2 cycles starting with Cycle 4[c]**	**EoS / ET**
Cycle Day	**-28 to -1 days**	**D1**	**D2**	**D4**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**±7 days**
Pharmacokinetic Samples											
Before infusion		X[d]			X[b]	X[b]		X[b]		X[b]	
End of infusion (90 minutes)[f]		X	X[j,k]	X[k]		X					
1 hour after end of infusion (150 minutes)[e,f]		X[j]									
3 hours after end of infusion (270 minutes) [e,f]		X[j]									
6 hours after end of infusion (450 minutes) [e,f]		X[j]									
Immunogenicity studies (ADA)[g]		X						X		X	X
Glycan analysis[h]		X			X	X		X		X	X
Biomarkers											
Globo H	X										
ADCC/CDC (humoral)[d,l]		X			X	X					
KIR, HLA, Fc receptor gamma genotyping[d]		X									
Multiplex IHC[n]	X										
Diagnostic marker[n]	X										

SSEA-3/SSEA-4[n]	X										
Surrogate biomarker[d,i]		X							X		

ADA = antidrug antibody; ADCC = antibody-dependent cell-mediated cytotoxicity; C = cycle; CDC = complement dependent cytotoxicity; D = day; EoS/ET = End of Study/Early Termination; HLA = human leukocyte antigen; IHC = immunohistochemistry; KIR = killer cell immunoglobulin-like receptor; SSEA = stage-specific embryonic antigens

Note: OBI-888 infusion should be administered on Days 1, 8, 15, and 22 of every 28 day cycle throughout the study treatment period.
The infusion duration of Cycle 1 and Cycle 2 are 90 minutes, and can be reduced to 30-60 minutes from Cycle 3, if there were no infusion related adverse events on prior infusions and at the discretion of the investigator.

a. Samples to be collected on Day 1 of C3, C5, C7, C9, C11, and C13.
b. Pre-infusion serum samples can be collected at any time prior to the infusion on the day of the infusion.
c. Samples to be collected on Day 1 of C4, C6, C8, C10, and C12.
d. C1D1 Pre-infusion serum samples can be drawn within 1 day prior-to the infusion.
e. If there is change of the infusion rate or interruption of infusion, the PK sampling at Day 1 are to be collected from the exact time of completion of infusion to obtain the post-infusion samples at 1, 3, 6 hour at the end of infusion. Exact time of sample collection and the reason for interruption should be documented in the eCRF.
f. Post infusion samples at the end of infusion and later (at 1, 3, and 6 hours after the end of the infusion) can be collected in a window of ±15 minutes
g. ADA sample will be collected along with the pre-infusion PK samples according to the above table. For patients with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.
h. Glycan analysis: Residual PK and ADA samples will be pooled for glycan analysis after PK and ADA data are finalized.
i. Samples should be collected to evaluate tumor-specific biomarkers (eg, CEA for colorectal, gastric, and esophageal cancer; and CA19-9 for pancreatic cancer).
j. This intensive PK sampling will be collected only from first 3 patients in each cohort.
k. For C1D2 and C1D4, samples can be collected in a window of ±2 hours:
    - 24 hours after end of infusion (for infusion at C1D1).
    - 72 hours after end of infusion (for infusion at C1D1).
l. Blood sample will be collected pre-infusion and end-of-infusion.
m. Blood sample will be collected pre-infusion.
n. Tumor biopsy samples obtained during the initial screening visit should be used for this assessment.

15. APPENDIX II IMPUTATION RULES FOR MISSING DATES

Algorithm for Treatment-emergent Adverse Events

AE Start Date	AE Stop Date	Action
Known	Known	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
	Missing or Unknown	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
Partial, but the known date components show that it cannot be on or after study drug start date	Known	Not TEAE
	Partial	Not TEAE
	Missing or Unknown	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day is unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing or Unknown	Assumed TEAE
Missing or Unknown	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day is unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing or Unknown	Assumed TEAE

Algorithm for Concomitant Medications

CM Start Date	CM Stop Date	Action
Known	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT
	Missing or Unknown	Assign as CONCOMITANT
Partial	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT
	Missing or Unknown	Assign as CONCOMITANT
Missing or Unknown	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT
	Missing or Unknown	Assign as CONCOMITANT

16. APPENDIX III. PHARMACOKINETIC ANALYSIS PLAN

PHARMACOKINETIC ANALYSIS PLAN

A PHASE I, OPEN-LABEL, DOSE ESCALATION AND COHORT EXPANSION STUDY EVALUATING THE SAFETY, PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD), AND THERAPEUTIC ACTIVITY OF OBI-888 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

VERSION 1.0

DATE: 29 JAN 2021

PHARMACOKINETIC ANALYSIS PLAN SIGNATURE PAGE

Pharmacokinetic Analysis Plan V1.0 (Dated 29JAN2021) for Protocol OBI-888-001.

	Name	Signature	Date
Author:			DDMMMYYYY
Position:			
Company:			

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:			DDMMMYYYY
Position:			
Company:			
Approved By:			DDMMMYYYY
Position:			
Company:			
Approved By:			DDMMMYYYY
Position:			
Company:			

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	29Jan2021	[redacted]	Not Applicable – First Version

TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS

Standard acronyms and abbreviations are listed below.

Abbreviation	Definition
AUC	Area Under the Concentration-Time Curve
AUC(0-last)	AUC to the Last Measurable Concentration
AUC(0-t)	AUC from 0 to time t
AUC(0-∞)	AUC Extrapolated to Infinity
BMI	Body Mass Index
BQL	Below the Quantification Limit
Clast	Last Measurable Concentration (above the quantification limit)
CL	Clearance
cm	Centimeter(s)
Cmax	Maximum Serum Concentration
CSR	Clinical Study Report
CV	Coefficient of Variation
EDC	Electronic Data Capture
g	Gram(s)
GM	Geometric Mean
GSD	Geometric Standard Deviation
h	Hour(s)
Ke	Terminal Phase Elimination Rate Constant
kg	Kilogram(s)
L	Liter(s)
LLOQ	Lower Limit of Quantification
Max	Maximum
Min	Minimum
min	Minute(s)
mL	Milliliter(s)
NCA	Noncompartmental Analysis
µg	Microgram(s)
PK	Pharmacokinetic(s)
SD	Standard Deviation
t1/2	Apparent Terminal Elimination Half-Life
Tlast	Time of Last Measurable Concentration
Tmax	Time to Maximum Serum Concentration (Cmax)
Vz	Apparent Volume of Distribution During Terminal Phase

1. INTRODUCTION

This **pharmacokinetic** analysis plan describes the rules and conventions to be used in the presentation and analysis of PK data to be presented for Protocol [OBI-888-001]. This document is based on protocol, version 4.0, dated 07 Jun 2019.

This document reiterates key PK elements in the study design of Protocol OBI-888-001and thoroughly describes the presentations and summaries of PK data as well as the noncompartmental analysis (NCA) to be included in the PK Report and summarized in the clinical study report (CSR) for this protocol. Shells and mockups are given for all PK-related tables, figures, and listings planned for inclusion in the CSR and/or PK Report. At minimum, mean PK plots as well as listings and summaries of OBI-888 concentrations and PK parameters will be included in the CSR, while all tables, figures, and listings described in this document will be included in the PK Report.

2. CLINICAL STUDY METHODS

2.1. Analysis Groups

This is a Phase I, open-label, dose-escalation (Part A) and cohort expansion (Part B) study of OBI-888, a humanized mAb targeting Globo H in patients with locally advanced or metastatic solid tumors. Part A is designed to establish the MTD and RP2D of OBI-888. Part B is intended to further characterize the safety and clinical activity profile of the RP2D dose of OBI-888 administered as monotherapy in patients with locally advanced or metastatic solid tumors.

2.2. Dose Administration

OBI-888 were administered as a 90-minute intravenous (IV) infusion on Days 1, 8, 15, and 22 of each 28-day cycle. The infusion duration may be reduced, at the investigator's discretion, to 30-60 minutes starting with Cycle 3 if the infusions in the first two cycles were well tolerated.

For Part A (Dose Escalation), OBI-888 will be given at the dose levels of 5, 10, and 20 mg/kg until MTD is determined. For Part B (Cohort Expansion), subjects were treated with 20 mg/kg OBI-888 since no DLTs have been observed at any dose level tested in Part A, and the MTD was not reached.

2.3. PK Sampling Schedule

Blood (serum) samples will be collected at the following time points: C1D1 Pre-infusion (within 1 day prior-to the infusion), post infusion samples at the end of infusion and at 1 (±15 min), 4 (±15 min), 8 (±15 min), 24 (± 2 h, on Day2), 72 (±2 h, on Day4) and 168 hours (any time prior to C1D2 infusion) after the end of the infusion.

2.4. Analytical Methods

The concentration of OBI-888 in the serum samples were determined using a validated ELISA method with an assay range of 468.75 to 30000 ng/mL.

3. PHARMACOKINETIC ANALYSIS METHODS

3.1. Analysis Population and Handling of Missing Time Points

The PK population will include all enrolled subjects who receive at least 1 dose of study drug and have sufficient PK samples (a sample at the end of administration and at least 3 samples during the elimination phase) to include in the PK assessments. Generally, only values above the lower limit of quantification (LLOQ) are used for the estimation of PK parameters. Unless otherwise specified below, missing sampling or concentration values should not be imputed, but left missing in the calculation of derived PK parameters. If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time may be used for the calculation of derived PK parameters. Collection of serum samples outside of the protocol defined time window for the time point will not result in exclusion of the sample result from NCA. Values below the lower limit of quantification (LLOQ) will be referred to as below the quantification limit (BQL). BQL values that precede the first PK concentration above the LLOQ will be imputed as 0 for linear plots and for all calculations including NCA and summary statistics. All other BQL values will be treated as missing for all analyses.

3.2. Demographic and Baseline Characteristics

Sex, race, age, weight, height, and body mass index (BMI) of subjects in the PK analysis population will be listed and summarized (PK Table 1, PK Listing 1).

3.3. Dosing and Pharmacokinetic Sampling Summary

Subject dose administration times will be presented (PK Listing 2). Cases that potentially affect the analysis will be discussed. Protocol deviations related to dosing or PK sampling will be listed (PK Listing 3) and summarized in the PK Report text. Deviations to be included in the PK Report include:

• Blood specimen not collected

• Plasma specimen result not obtained

• Specimen temperature excursion

• Required specimen collected out of window

• Any other deviation determined by the PK analyst to be potentially affect PK

Drug plasma concentrations will be listed by subject (PK Listing 4), with nominal and actual time

associated with the sample indicated (nominal time is defined as the time in h since the start time of the dose). Both laboratory reported concentration values, and modified concentration values used for analysis (for instance, imputation of 0 for a BQL value at baseline) will be included, as separate columns, in the listing. Plasma drug concentrations will also be summarized (PK Table 2) and plotted. PK Figure 1 and PK Figure 2 will plot all individual subject plasma PK profiles, as linear and semi-logarithmic plots, respectively. Subject ID for each individual profile in these figures will be shown in a legend.

3.4. Definition and Estimation of Individual NCA PK Parameters

PK parameters will be estimated through a NCA using version 8.2 or later of Phoenix® WinNonlin® (Pharsight Corporation, Cary, NC). Actual post-dose time will be used for the estimation of PK parameters instead of nominal time. Individual PK parameter estimates will be listed (PK Listing 5).

Phoenix® WinNonlin® NCA will use the following settings to compute parameters from plasma PK data:

• Linear Up Log Down calculation method

• Uniform weighting

• Intravenous dose

• Plasma Model Type

• Lambda Z Acceptance Criteria

- Rsq adjusted ≥ 0.80
- Span ≥ 2.0 half-lives
- Includes ≥ 3 timepoints after Tmax

T_{max} (hour): Time to reach the maximum concentration

- directly taken from the observed concentration

C_{max} (µg/mL): Maximum concentration

- directly taken from the observed concentration

C_{last} (µg/mL): Concentration at last quantifiable time point

- directly taken from the observed concentration

λ (1/h): Elimination rate constant associated with the terminal phase

- estimated terminal slope of the linear regression of log-transformed concentration vs time
- The regression analysis should contain data from at least 3 different time points in the terminal phase and as many data points as possible, always including the last quantifiable concentration but excluding the concentration at T_{max}.
- The coefficient of determination Adj_RSq^2 should be larger than or equal to 0.80. If at least one of these three conditions is not fulfilled, the terminal half-life and the parameters depending on t½ will be listed but flagged as not reliably calculated. They will generally be excluded from descriptive statistics and statistical testing procedures.

$t_{½}$ (h): Terminal elimination half-life

- $t_{1/2} = \frac{log_e 2}{\lambda}$

AUC_{last} (h*µg/mL): Area under the concentration-time curve from time zero to time the last quantifiable time, calculated by log-linear trapezoidal rule.

AUC_{∞} (h*µg/mL): Area under the concentration-time curve from time zero to infinite time

- The percentage of extrapolated AUC should not exceed 20% of AUC∞ for each individual profile. If the percentage of extrapolated AUC is more than 20%, the individual AUC∞ result and the parameters depending on AUC∞ will be listed but flagged as not reliably calculated. They will generally not be included in descriptive statistics and statistical testing procedures.

$AUMC_{last}$ (h^2*µg/mL): Area under the first moment of the concentration time curve from time zero to time the last quantifiable time, calculated by log-linear trapezoidal rule.

$AUMC_{\infty}$ (h^2*µg/mL): Area under the first moment of the concentration-time curve from time zero to infinite time

CL (mL/h): Total body clearance following iv administration

- $CL = \frac{Total\ Dose\ Administrated\ in\ "\mu g"}{AUC_{\infty}}$

V_z (mL): Volume of distribution following iv administration

- $V_z = {CL}/{\lambda}$

V_{ss} (mL): Volume of distribution at steady-state following iv administration

- $V_{ss} = \frac{Total\ Dose\ Administrated\ in\ "\mu g" \times AUMC}{(AUC_{\infty})^2}$

Dose proportionality

- To investigate the dose proportionality of AUC and Cmax, a statistical analysis using the power model will be conducted. The power model will have the form:
- $Y = a*(dose)^b$, where Y is the PK parameter, and a and b are the coefficient and exponent, respectively, of the power equation.
- By taking the natural logarithm (ln), the power model can be analyzed using linear regression and has the form:
- $\ln(Y) = \ln(a)+b*\ln(dose) + error = \alpha + \beta*\ln(dose) + error$,
- where α is the intercept, and β is the slope, and ln(dose) is based on the dose size for each subject.
- Estimates of slope and intercept along with their 90% confidence intervals will be reported. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality using the power model.

All calculations will use the actual post-dose times recorded on the CRF. All computed PK parameters will be listed by subject and summarized by dose group in the Escalation Phase and by disease cohort in the Expansion Phase (mean, standard deviation, coefficient of variation, minimum, maximum, number of observations). Individual and mean (by time) concentrations versus time will be plotted for each dose on both linear and natural logarithm scales.

3.5. Descriptive Statistics

Subject-specific PK parameter estimates will be listed (PK Listing 5). PK estimates will be summarized in PK Table 3. Summary statistics will include mean, standard deviation (SD), minimum, maximum, median, coefficient of variation as a percent (CV%), GM, and geometric standard deviation (GSD)

4. LISTING OF PROPOSED TABLES, FIGURES, AND LISTINGS

PK Table 1: Summary of Demographic and Baseline Characteristics of Subjects Included in the PK Analysis Population

Parameter	**PK Analysis Population (N=X)**
Sex – N (%)	
Male	
Female	
Age (years)	
Mean (SD)	
Median	
Min, Max	
Height (cm)	
Mean (SD)	
Median	
Min, Max	
Weight (kg)	
Mean (SD)	
Median	
Min, Max	
BMI (kg/m2)	
Mean (SD)	
Median	
Min, Max	
Race – N (%)	
American Indian or Alaska Native	
Asian	
Black or African American	
Native Hawaiian or other Pacific Islander	
White	

PK Table 2: Summary Statistics for Concentrations by Nominal Time

Subject ID	**OBI-888 Concentration (µg/mL) by Nominal Time[1] After Dose (h)**							
	0	1.5	2.5	4.5	7.5	25.5	73.5	169.5
UXX-001	x	x	x	x	x	x	x	x
UXX-002	x	x	x	x	x	x	x	x
UXX-003	x	x	x	x	x	x	x	x
…	x	x	x	x	x	x	x	x
Statistics								
N_2	x	x	x	x	x	x	x	x
Mean	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
SD	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
GM	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)	(x, x)

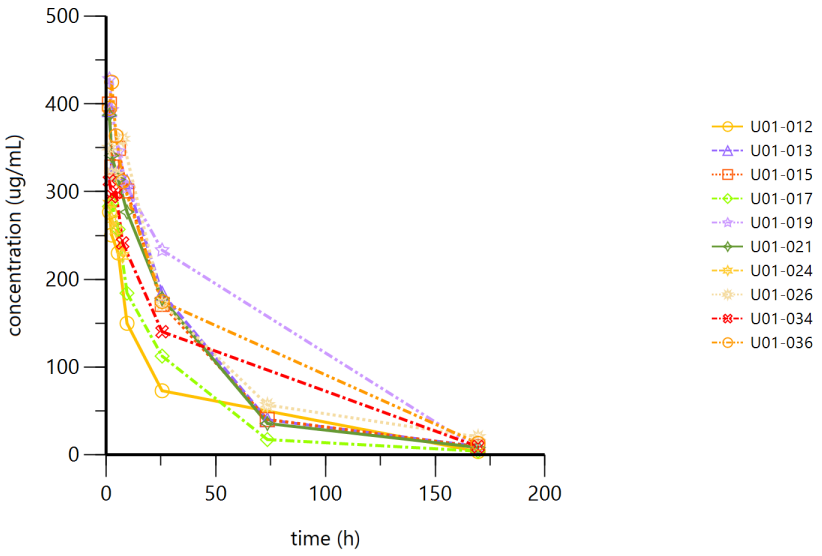
1 Times are relative to time of dosing.
2 Number of data points used to compute the summary statistics. For calculation of summary statistics, BQL values were imputed as 0 if they did not come after a PK sample concentration that is above the LLOQ and treated as missing otherwise.

PK Table 3: Summary Statistics for PK Parameters

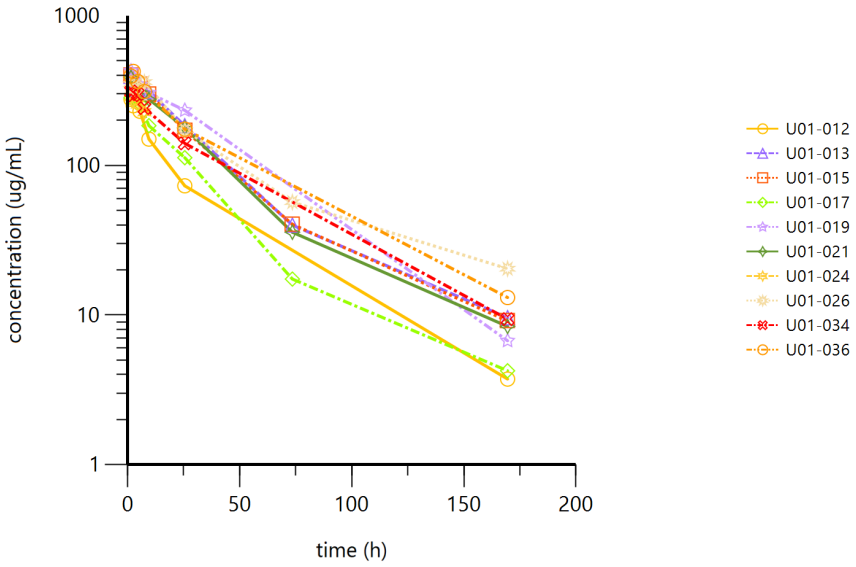
Statistic	T_{max} (h)	C_{max} (µg/mL)	C_{max_D} (µg/mL/mg)	$AUC_{(0\text{-}last)}$ (h×µg/mL)	$AUC_{(0\text{-}last)\_D}$ (h×µg/mL/mg)	CL (L/h)	K_e (1/h)	$t_{1/2}$ (h)	Vss (L)
N									
Mean									
SD									
Min									
Median									
Max									
CV %									
GM									
GSD									

APPENDIX 1. LIST OF PROPOSED PK FIGURES LIST OF PK FIGURES

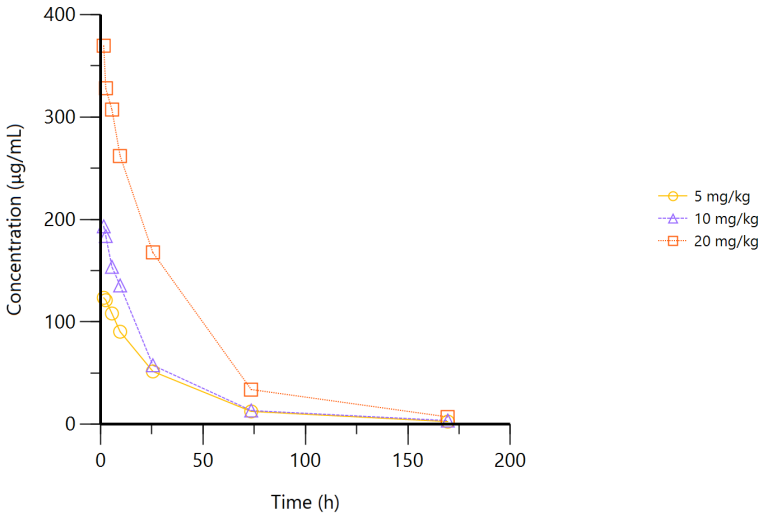
PK Figure 1: Concentration Profiles for All Subjects by Time



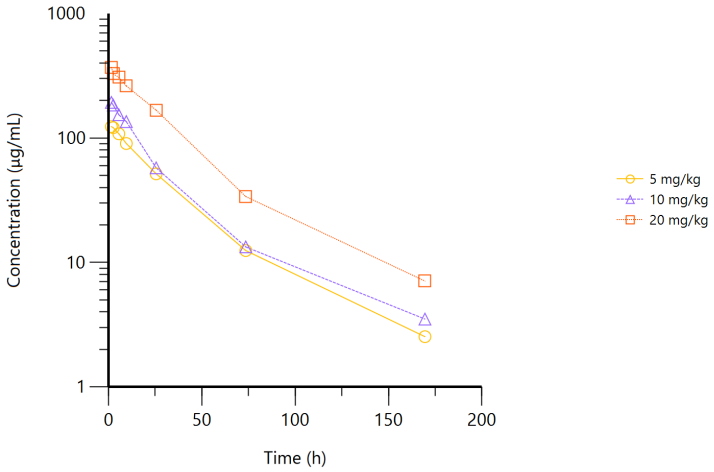
PK Figure 2: Semi-log Concentration Profiles for All Subjects by Time



PK Figure 3: Mean Concentration by Nominal Time



PK Figure 4: Mean Concentration by Nominal Time (Semi-Log)



APPENDIX 2. LIST OF PROPOSED PK LISTINGS TABLE OF PK LISTINGS

PK Listing 1: Subject Level Demographic and Baseline Characteristics

Subject ID	Sex	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
UXX-001						
UXX-002						
UXX-003						
…..						

PK Listing 2: OBI-888 Dosing

Subject ID	Dose (mg)	Date of Infusion	Start Time	End Time

PK Listing 3: Protocol Deviations Related to Dosing or PK Samples

Subject ID	DV Number	Deviation Description	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Specimen Type	Affected Visit Number	Deviation Category

Note: This listing contains a subset of the protocol deviations in the clinical database relevant to the PK analysis

PK Listing 4: Subject Level OBI-888 Concentrations in Plasma

Subject ID	Nominal Time1 (h)	Actual Time1 (h)	Lab Reported Drug Concentration (µg/mL)	Analysis Drug Concentration (µg/mL)	Used in Ke Calculations	Excluded from NCA	Reason for Exclusion from NCA
UXX-001	0	0	BQL	0	No	No	
UXX-002	0.5	0.5	50.1	50.1	No	No	
UXX-003	1.5	1.52	BQL	missing	No	No	
…							

1Times are relative to time of dose. For Actual Times, out-of-window times are indicated by an asterisk

PK Listing 5: Subject-Specific Pharmacokinetic Parameters

Subject ID	T_{max} (h)	C_{max} (µg/mL)	C_{max_D} (µg/mL/mg)	$AUC_{(0\text{-}last)}$ (h×µg/mL)	$AUC_{(0\text{-}last)\_D}$ (h×µg/mL/mg)	CL (L/h)	K_e (1/h)	$t_{1/2}$ (h)	Vss (L)
UXX-001									
UXX-002									
UXX-003									
…									