OBI Pharma, Inc

STATISTICAL ANALYSIS PLAN

PROTOCOL OBI-999-001

A Phase 1/2, Open-Label, Dose-Escalation and Cohort-Expansion Study Evaluating the Safety, Pharmacokinetics, and Therapeutic Activity of OBI-999 in Patients With Advanced Solid Tumors

Protocol code:	OBI-999-001
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SAP Author:	[redacted]
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Pharmacokinetic Analysis Plan Author	[redacted]

1. DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
Final 1.0	21-APR-2023
Final 2.0	12-JUL-2024

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).	On 10Nov2023 Sponsor stated they stop the OBI-999-001 study and elected to generate an aCSR.
	3.0	Sentence added about aCSR.	To clarify the scope of the TFLs that will be generated.
	5.4	Sentence "The description above represents the initial interim analysis planning based on the protocol. In reality at the end of the first stage of Part B, four patients did not have a RECIST post-baseline assessment and so it has been decided to replace them to have enough data to perform the go/no-go analysis. 2 'replacement' patients have been enrolled in the pancreatic cohort, while searching for 2 'replacement' patients in the colorectal cohort was in progress. On 10th November 2023, Sponsor stated they stop the study and elected to generate an aCSR and so formal go/no-go analysis never happened." added.	To clarify about the go/no-go analysis.
	8.0	Sentence "Analysis endpoints are listed as per protocol. Only those endpoints marked with * will be analyzed in aCSR as per sponsor	To clarify responsibilities

		decision. Exploratory analyses will be conducted by OBI Translational Biology (or their designee) and may be included in the aCSR" added.	
	8.1—8.3	Added asterisks to show which endpoints will be analyzed.	The aCSR will not include all endpoints planned in the protocol.
	10.7	Sentence "Only those analyses marked with * will be analyzed in aCSR as per sponsor decision." added.	The aCSR will not include all endpoints planned in the protocol.
	10.7.1	Sentences "Only Those AEs marked with * will be analyzed in the aCSR as per sponsor decision.".	The aCSR will not include all adverse events planned in the SAP version 1.0.
	10.7.1	Added asterisks to show which adverse events will be analyzed and listed.	The aCSR will not include all adverse events planned in the SAP version 1.0.
	10.7.1	Added asterisks to show which analyses will be conducted.	The aCSR will not include all endpoints planned in the protocol.
	11	Sentence added about aCSR.	To clarify the scope of the TFLs that will be generated.

APPROVAL SIGNATURES

STUDY TITLE: A Phase 1/2, Open-Label, Dose-Escalation and Cohort-Expansion Study Evaluating the Safety, Pharmacokinetics, and Therapeutic Activity of OBI-999 in Patients With Advanced Solid Tumors

PROTOCOL NUMBER: OBI-999-001 (V 7.0, 21-July-2021)

SAP Final 2.0, 12-JUL-2024

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
aCSR	abbreviated Clinical Study Report
ADAs	anti-drug antibodies
ADC	antibody-drug conjugate
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BOR	Best overall response
CBR	clinical benefit rate
CI	Confidence interval
CR	complete response
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of variation
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Monomethyl auristatin E
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
ORR	objective response rate
PCSA	Potentially clinically significant abnormality
PD	pharmacodynamic / progressive disease (depending on context)
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease / standard deviation (depending on context)
SOC	System Organ Class
SRC	Safety review committee
TEAE	treatment-emergent adverse event

WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol OBI-999-001 final version 7.0 (dated 21 July 2021), and electronic case report form (eCRF) production of 13 December 2021.

On 10 November 2023, Sponsor stated they stop the OBI-999-001 study and elected to generate an abbreviated Clinical Study Report (aCSR).

4. STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVES

The primary objectives are:

- To determine the safety and tolerability of OBI-999 when administered intravenously (IV) to patients with advanced solid tumors.
- To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of OBI-999.

4.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the preliminary clinical activity profile of OBI-999 (objective response rate [ORR], clinical benefit rate [CBR], duration of response [DOR], and progression-free survival [PFS]).
- To evaluate the immunogenicity of OBI-999 (anti-drug antibodies [ADAs]).
- To determine the serum pharmacokinetics (PK) of OBI-999 and its active metabolite monomethyl auristatin E (MMAE).

4.3 EXPLORATORY OBJECTIVE

The exploratory objective is:

- To explore potential predictive biomarkers of OBI-999 activity.

5. STUDY DESCRIPTION

5.1 STUDY DESIGN

This is a Phase 1/2, open-label, dose-escalation, and cohort-expansion study of OBI-999, an antibody-drug conjugate (ADC)-targeting Globo H in patients with advanced solid tumors.

This is a 2-part study. Part A (Dose-Escalation) is designed to establish the MTD and RP2D of OBI-999 as monotherapy. Part B (Cohort-Expansion) is intended to further characterize the safety and preliminary clinical activity profile of the RP2D of OBI-999 in patients with advanced solid tumors.

5.1.1 PART A – DOSE-ESCALATION

Twenty-two patients with advanced solid tumors were enrolled in Part A. No Globo H expression testing was required for inclusion.

Five cohorts of escalating dose levels of 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg (capping calculations at a maximum of 100 kg) OBI-999 were planned to be enrolled and assessed using a 3+3 design to identify the MTD and RP2D. The RP2D of OBI-999 was determined to be 1.2 mg/kg (capping administered dose to a maximum of 120 mg for 100 kg) administered on Day 1 of each 21-day cycle.

Three patients were enrolled at the lowest dose level. If none of the 3 patients experienced a dose-limiting toxicity (DLT) in the first 21-day cycle, the next cohort of 3 patients was 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, the next cohort of 3 patients was 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 the lower dose level was designated the MTD, where no more than 1 of 6 patients 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 considered the MTD if ≤ 1 in 6 patients had a DLT.

A patient who withdraws from the study within the DLT evaluation period for reasons other than drug-related adverse event (AE) were replaced.

Escalation to higher OBI-999 dose cohorts is not permitted during the study. After a DLT is experienced by a patient, dose interruption, modifications, or dose delays may apply, as per Investigator judgement (refer protocol Section 8.3).

Patients will continue to receive treatment with OBI-999 until disease progression, unacceptable toxicity, consent withdrawal, or for up to 35 cycles (approximately 2 years), whichever occurs first.

5.1.2 STOPPING RULES

The Sponsor, Investigator (following consultation with the Sponsor), or regulatory officials (regulatory agency or an Institutional Review Board [IRB]/ Independent Ethics Committee [IEC]) have the right to prematurely discontinue or suspend the study or investigational site at their discretion, at any time, if study and/or site conditions warrant. This action may be taken after appropriate consultation among the Sponsor, Investigator, and clinical monitor. The reasons for such action may include, but are not limited to the following:

- Safety concerns, such as more than one third of the patients within a dose cohort have one of the following:
    - ≥ Grade 3 systemic infusion reactions (despite pre-medication),
    - Grade 4 DLTs (Refer to Protocol Section 6.2), or
    - Related serious adverse events (SAEs) (Refer to Protocol Section 8.2.3 & 8.3.1.1)
- The Investigator does not comply with the protocol, Good Clinical Practice (GCP), and/or any contract between the Investigator and Sponsor, including Contract Research Organizations (CROs) and subsidiaries thereof.

In the circumstance of such an event, the Sponsor reserves the right to halt and review this study and will discuss with the Investigator (including the reasons for taking such action) about dose modification, amendment to protocol, or study stopping. Final decision about continuing, termination or any other change in the study would remain with the Sponsor.

5.1.3 PART B-COHORT-EXPANSION

Up to 57 additional patients with advanced solid tumors that have high Globo H expression (defined as an H-score ≥ 100 using a validated immunohistochemistry [IHC] assay) will be enrolled in Part B using a Simon's two-stage cohort expansion design. Part B will be conducted to obtain additional safety data, characterize the PK profile of OBI-999, and obtain a preliminary assessment of the clinical activity profile of OBI-999 in Globo H expressing advanced solid tumors.

Patients enrolled in Part B will receive the RP2D dose of 1.2 mg/kg (capping calculations at a maximum of 100 kg) OBI-999 on Day 1 of each 21-day cycle.

The following 3 cohorts of patients who have high expression of Globo H by a qualified laboratory assessment (Globo H H-score ≥ 100 using a validated IHC assay) will be enrolled in Part B.

- Cohort 1: Pancreatic cancer
- Cohort 2: Colorectal cancer
- Cohort 3: Basket (any solid tumor types other than those included in Cohorts 1 and 2)

Patients will continue to receive treatment with OBI-999 until disease progression, unacceptable toxicity, consent withdrawal, or for up to 35 cycles (approximately 2 years), whichever occurs first.

5.1.4 STUDY DURATION

The study (Parts A and B) will include a screening period (up to 28 days), a treatment period, and a follow-up period.

Patients will continue to receive treatment with OBI-999 until disease progression, unacceptable toxicity, consent withdrawal, or for up to 35 cycles (approximately 2 years), whichever occurs first. Patients will be followed up to the 24-week scheduled response assessment for the purposes of counting objective responses for Simon's two-stage design success criteria.

The safety follow-up visit will be conducted 28 days after the last dose of study treatment.

5.2 STUDY TREATMENT

For Part A (Dose-Escalation), OBI-999 was planned to be given at doses of 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg (capping calculations at a maximum of 100 kg) using a 3+3 design to identify the MTD and RP2D.

For Part B (Cohort-Expansion), OBI-999 will be given at the RP2D of 1.2 mg/kg (capping administered dose to a maximum of 120 mg for 100 kg).

OBI-999 investigational drug solution (OBI-999 drug product mixed with saline/glucose infusion solution) will be administered on Day 1 of each 21-day cycle by the site staff. The infusion should be given for a duration of approximately 60 minutes (± 10 minutes), for the initial 2 cycles (Cycle 1 and Cycle 2). The infusion duration for Cycles 3 and beyond may be reduced, at the Investigator's discretion, to 30 minutes if no infusion related AEs occur during the first 2 cycles.

Treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or for up to 35 cycles (approximately 2 years), whichever occurs first.

5.3 SAFETY REVIEW COMMITTEE

The safety review committee (SRC) for this study will be comprised of the clinical lead, medical monitor, and the Investigator(s) or designee. The SRC will act in an advisory capacity to monitor

patient safety and efficacy during the trial and its activities will be defined in a separate SRC charter.

This SRC convened after each cohort completed the first cycle of treatment during Part A (Dose-Escalation), to review safety data (AEs and laboratory toxicities) and to determine whether DLTs occurred.

The RP2D for Part B (Cohort-Expansion) was determined by the SRC based on both the frequency of DLTs observed during Cycle 1 according to the 3+3 design, and also by the frequency and severity of cumulative toxicities such as peripheral neuropathy. The SRC will continue to monitor the severity and frequency of acute and cumulative toxicities at regular intervals, i.e., every 3 months, to ensure acceptable tolerability of the selected RP2D and of the effectiveness of dose modification rules. The SRC will receive updated tabulations of recruitment, AEs, SAEs, clinical laboratory events, and dose modifications which will serve as the basis for their assessments.

5.4 INTERIM ANALYSIS

There will not be any other formal interim analyses except for the one related to Simon's two stage design described below; however, a description of the Dose-Escalation Phase and the selection of the RP2D may be written up for the purposes of a manuscript.

Moreover, the cohort expansion portion of the study (Part B) will enrol up to 57 patients based on Simon's two-stage design. The first stage will recruit up to 9 patients in each of three cohorts. If at least one objective response is observed, a second stage recruitment will occur with up to 10 additional patients enrolled into that cohort, for a total of up to 19 patients per cohort. If at least 4 objective responses are observed in the 19 patients, then OBI-999 will be considered worthy of further evaluation in that indication. Patients will be followed up to the 24-week scheduled response assessment for the purposes of counting objective responses for Simon's two-stage design success criteria. A formal analysis will be performed to support it.

Patient enrolment, patient disposition, baseline characteristics, cancer history, clinical benefit rate, exposure to OBI-999, AE and ECG summaries (all described in this document) will support this formal analysis at end of stage 1.

If Simon's two-stage design success criteria is not met, then the second stage recruitment will not occur, and analyses will be done for supporting an aCSR.

The description above represents the initial interim analysis planning based on the protocol. In reality at the end of the first stage of Part B, four patients did not have a RECIST post-baseline assessment and so it has been decided to replace them to have enough data to perform the go/no-go analysis. 2 'replacement' patients have been enrolled in the pancreatic cohort, while searching for 2 'replacement' patients in the colorectal cohort was in progress. On 10th November 2023, Sponsor stated they stop the study and elected to generate an aCSR and so formal go/no-go analysis never happened.

6. RANDOMIZATION AND BLINDING

The study is a Phase 1/2 open-label, dose escalation and cohort expansion study and does not involve randomization; patients and members of the clinical study team will not be blinded to treatment.

7. SAMPLE SIZE AND POWER CALCULATION

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

Up to 30 patients were to have been enrolled in the 3+3 dose-escalation portion of the study (Part A).

The cohort-expansion portion of the study (Part B) will enroll up to 57 patients based on Simon's two-stage design. The first stage will recruit up to 9 patients in each of three cohorts. If at least 1 objective response is observed, a second stage recruitment will occur with up to 10 additional patients enrolled into that cohort, for a total of up to 19 patients per cohort. If at least 4 objective responses are observed in the 19 patients, then OBI-999 will be considered worthy of further evaluation in that indication. Patients will be followed up to the 24-week scheduled response assessment for the purposes of counting objective responses for Simon's two-stage design success criteria. This design is based on a level of low interest for a treatment with an ORR of 10% versus a level of high interest for a treatment with an ORR of 25%. The sample size is based on a one-sided alpha of 0.12 and 72% 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 aCSR as per sponsor decision. Exploratory analyses are to be conducted by OBI Transnational Biology (or their designee) and may be included as appendices in the aCSR.

8.1 PRIMARY ENDPOINTS:

Part A (Dose-Escalation):

- AEs/ SAEs and laboratory abnormalities as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0*.
- DLTs with OBI-999*.
- MTD and RP2D of OBI-999.

Part B (Cohort-Expansion):

- Percentage of patients with objective response*, clinical benefit, DOR and PFS according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
- Percentage of patients with ADAs in blood*.

8.2 SECONDARY ENDPOINTS:

Part A (Dose-Escalation):

- PK parameters of OBI-999 and its active metabolite MMAE*.

Part B (Cohort-Expansion):

- AEs/SAEs and laboratory abnormalities as graded by NCI CTCAE version 5.0*.
- PK parameters of OBI-999 and its active metabolite MMAE*.

8.3 EXPLORATORY ENDPOINTS:

Part A (Dose-Escalation):

- Potential predictive biomarkers for OBI-999 activity such as expression of Globo H and other tumor-associated glycans or tumor molecular phenotypes.

Part B (Cohort-Expansion):

- Potential predictive biomarkers for OBI-999 activity such as expression of Globo H and other tumor-associated glycans or tumor molecular phenotypes.

9. ANALYSIS POPULATIONS

Screen Failures Set: all patients who are considered screening failures. This analysis set will allow comparison of demographic and baseline characteristics for screen failures versus enrolled patients, to demonstrate that those who were excluded from the study were no different from those who had qualified and that there were no systemic biases in the enrollment of the study.

Screened Population: all patients who have signed informed consent.

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

Efficacy population: all enrolled patients who received at least one dose of study drug and had at least one follow-up tumor assessment scan. The efficacy population will be used as primary for analysis of clinical activity.

PK population: all enrolled patients 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. 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 performed, 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 [SD], 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. Descriptive summaries of time to event data will include medians and confidence intervals.

All data will be listed for all patients.

Frequency distributions (counts and percentages) together with mean and SD of ordinal scores will be presented for categorical variables. Discrete variables that are ordinal scaled (e.g., Eastern Cooperative Oncology Group [ECOG] performance score) will additionally be presented with mean scores and SD. 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 given in section 9.3.

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-999 dose (0.4, 0.8, 1.2, and 1.6 mg/kg) cohorts and overall. The following cohorts and overall will be presented:

- OBI-999 0.4 mg/kg
- OBI-999 0.8 mg/kg
- OBI-999 1.2 mg/kg
- OBI-999 1.6 mg/kg
- Dose-Escalation Total

OBI-999 2.0 mg/kg was planned but Part A was closed before this dose was administered, and therefore there no patients in this cohort. For this reason, this cohort will not be presented in any of the analyses.

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

- Cohort 1: Pancreatic cancer
- Cohort 2: Colorectal cancer
- Cohort 3: Basket (any solid tumor type other than those included in Cohorts 1 and 2)
- Cohort-Expansion Total

10.2 Definition of Baseline, Study Visits, and Visit Windows

Baseline for each assessment is defined as the last non-missing assessment prior to first dose of study drug. If scheduled and unscheduled assessments occurred on the same day and they both can qualify for being baseline, the value from the scheduled assessment should be considered as baseline. The baseline will be presented for each part.

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

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 in the listings.

For ORR endpoint, patients with missing data (for any reason) will be included as non-responders in the statistical analysis for each related follow-up analysis. For analyses performed in the safety population, patients who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders and retained in the denominator.

For CBR endpoint, patients with missing data (for any reason) will be included as non-responders in the statistical analysis for each related follow-up analysis.

10.4 Patient Disposition

The number of patients screened and the reasons for screen failure from main consent, including

exclusion criteria met and inclusion criteria not met, will be tabulated overall in the screened population (all patients who have signed main informed consent) by Parts A and B.

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 with number of enrolled patients, will be tabulated as indicated in section 9.1. The number and percentage within each category will be presented by Parts A and B and by cohort (by dose level in Part A and by cancer type in Part B).

The number and percentage of patients included in the safety, efficacy and PK populations will also be conducted by study part and by cohort (by dose level in Part A and by cancer type in Part B).

A listing with all enrolled patients (all patients who have been screened and are eligible) will be generated for the study to describe country/study center, patient number, study part, cohort, date of Globo-H screening consent, Globo-H screening consent version, date of main informed consent, informed consent version, was informed consent withdrawn, date of withdrawal, first and last study drug dosing dates, total duration of study drug dosing, the reason for discontinuing study drug dosing, end of study (completion or discontinuation) date, and reason for discontinuing the study.

10.5 PROTOCOL DEVIATIONS

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

The number and percentage of patients with at least one major protocol deviation and the categories of the major protocol deviations will be summarized by study part and by cohort (by dose level in Part A and by cancer type in Part B) using the safety and efficacy populations.

The number and percentages of patients with at least one major protocol deviation related to COVID-19 will be summarized too.

Protocol deviations related to COVID-19 will be listed.

10.6 PATIENT CHARACTERISTICS

Baseline and demographic characteristics will be summarized for the screen failures population and by study part and by cohort (by dose level in Part A and by cancer type in Part B) using the safety population. Medical history, prior and concomitant medications will be summarized by study part and by cohort (by dose level in Part A and by cancer type in Part B) using the safety and efficacy populations.

10.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Descriptive statistics for continuous variables (age at screening, height at screening, weight at baseline, body mass index [BMI] at baseline, and Globo H score) and frequency counts and percentages for categorical demographic variables (child-bearing status, sex, ethnicity, race, Globo H [positive/negative] and ECOG performance) will be summarized by study part, and by

cohort (by dose level in Part A and by cancer type in Part B) using the safety and efficacy populations.

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.

Baseline and demographic characteristics will be provided in a listing.

10.6.2 Medical History and Current Medical Conditions

Medical history (conditions not ongoing at screening) and concomitant conditions (ongoing at screening or unknown) will be coded using Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 23.0 or newer. The number and percentage of patients reporting a history of any medical condition, as recorded on the eCRF, will be summarized by study part, by cohort (by dose level in Part A and by cancer type in Part B), by System Organ Class (SOC) and preferred term (PT) in the safety and efficacy populations. Patients having the same medical condition (based on SOC and PT) more than once will be counted only once for a particular SOC and PT.

Medical history, disease characteristics, surgical and medical procedures will be listed.

10.6.3 Prior and Concomitant Medications

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study will be documented as AEs on the eCRF.

All prior and concomitant medications will be coded using September 2019 Format Global B3 version of World Health Organization Drug Dictionary Enhanced (WHO-DD) and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code. The exact version of the dictionary is subject to change.

The number and percentages of patients with at least one prior or concomitant medication will be summarized by ATC level 4 and ATC level 2 classes and WHO-DD preferred term (PT). Prior and concomitant medications will be summarized by study part, and by cohort (by dose level in Part A and by cancer type in Part B) in the safety and efficacy populations. These summaries will be done separately.

A medication is considered prior if the end date of the medication is prior to the first study drug dose date. A medication is considered concomitant if it is administered before the first study drug dose date and is continuing at the time of the first dose of study drug, or if it is administered on or after the first study drug dose date up to 28 days after patient’s last study drug dose.

Patients receiving the same medication more than once will be counted only once for a particular medication class, where applicable.

Medications having both start and end dates missing will be considered concomitant; in the case of a missing start date and not a missing end date the medication will be considered concomitant unless the end date is prior to the date of the first dose.

All prior and concomitant medications will be provided in a listing.

10.6.4 Cancer history

Location of primary tumor, histological/molecular subtype of cancer, elevation of tumor-specific serum markers observed prior to study entry, tumor marker elevated (if elevation observed), TNM stage at study entry, TNM stage at diagnosis of advanced disease, metastatic sites and previous cancer therapies will be tabulated. Data will be summarized in the safety and efficacy populations by study part, and by cohort (by dose level in Part A and by cancer type in Part B).

Cancer history will be listed.

10.6.5 Other Medical History

Medical history terms, start/end dates, ongoing status, active treatment at study entry will be presented in a listing.

10.6.6 Prior Cancer Surgeries

Prior cancer surgery description and date will be presented in a listing.

10.6.7 Prior Cancer Radiotherapy

Radiation field (anatomic site), first and last dose dates, and total dose with units will be presented in a listing.

10.6.8 Prior Cancer Medication Therapy

Treatment setting, best response to treatment, and reason to stop treatment will be tabulated. Data will be summarized in the safety and efficacy populations by study part, and by cohort (by dose level in Part A and by cancer type in Part B).

Prior cancer medication therapies will be presented in a listing.

10.6.9 Smoking History

Substance type, usage status, frequency, length of usage and smoking exposure will be tabulated; descriptive statistics for continuous variable (‘Number used’ eCRF field) will be summarized by study part, and by cohort (by dose level in Part A and by cancer type in Part B) using the safety and efficacy populations.

Length of usage, presented in years, will be calculated as the difference in stop and start dates of usage/365.25.

Quantification of smoking exposure will be expressed as “pack-years”. Pack-years will be calculated as follows: number of years participant smoked*number of cigarettes smoked per day divided by 20. The following rules will be applied to calculate “pack-years”:

- 1 pipe = 2.5 cigarettes.
- 1 cigar = 2.5 cigarettes.
- 20 cigarettes a day for 1 year = 1 pack-year.
- 8 pipes a day for 1 year = 1 pack-year.
- 8 cigars a day for 1 year = 1 pack-year.

Smoking history will be provided in a listing.

10.7 ANALYSIS OF STUDY ENDPOINTS

This section describes analysis of primary, secondary and exploratory endpoints as per protocol. All endpoints will be analyzed using planned treatments. Summaries will be presented for safety population in Part A and Part B. Summaries for anti-OBI 999 antibodies (ADA) in Part B will be presented in PK and safety populations.

Only those analyses marked with * will be analyzed in aCSR as per sponsor decision.

10.7.1 PRIMARY ENDPOINTS

PART A (DOSE-ESCALATION)

A. AEs/ SAEs and laboratory abnormalities as graded by NCI CTCAE version 5.0*.

Treatment emergent adverse events (TEAEs) are defined as AEs with onset dates on or after the start of study drug until 28 days after the last dose 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.

TEAEs will be summarized by study part, cohort (by dose level in Part A and by cancer type in Part B), SOC, 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. The summaries will be sorted by decreasing order of overall incidence of SOCs and decreasing order of overall incidence of PTs within SOCs.

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 respective treatment.

Overview summaries of the number and percentages of patients and number of events within the following categories will be provided by study part and by cohort (by dose level in Part A and by cancer type in Part B):

- Any TEAE
- Any TEAE grade ≥ 3
- Any TEAE related to OBI-999
- Any Serious TEAE
- Any Non-Serious TEAE
- Any Serious TEAE related to OBI-999
- Any TEAE leading to death
- Any TEAE leading to discontinuation of OBI-999 (defined as AE with an action taken equals to “Drug Withdrawn”)
- Any Serious TEAE leading to discontinuation of OBI-999 (defined as AE with an action taken equals to “Drug Withdrawn”)
- Any TEAE leading to study discontinuation (defined as AE flagged as Grade 4 infusion reactions and OBI-999 related toxicity, or intercurrent illness in the “End of Study” eCRF

page)
- Any Serious TEAE leading to study discontinuation (defined as AE flagged as Grade 4 infusion reactions and OBI-999 related toxicity, or intercurrent illness in the “End of Study” eCRF page)

Tables by SOC and PT will be displayed for following AEs. Only those AEs marked with * will be analyzed in the aCSR as per sponsor decision.

- TEAEs*
- TEAEs grade ≥ 3*
- TEAEs related to OBI-999*
- Serious TEAEs*
- Non-Serious TEAEs
- Serious TEAEs related to OBI-999*
- TEAEs leading to death*
- TEAEs leading to discontinuation of OBI-999*
- Serious TEAEs leading to discontinuation of OBI-999*
- TEAEs leading to study discontinuation*
- Serious TEAEs leading to study discontinuation*

Tables by SOC and PT will display the incidence of events (number of events, number and percentage of patients with any event, number of events of each specific SOC, number and percentage of patients with any event of each specific SOC, number of events of each specific PT and number and percentage of patients with any event of each specific PT).

Tables of TEAEs and serious TEAEs by SOC, PT and worst CTCAE grade (per summarization level) will be presented and will display number and percentage of patients with any event of each specific SOC/PT/CTCAE grade. Number of events will not be displayed. If a patient has multiple AEs with the same SOC or SOC and PT respectively and one of them has missing severity, the highest severity will be used. If the severity is missing for all AEs with the same SOC or SOC and PT, a “missing” category will be added in the summary table.

The following listings will be prepared for AEs. Only those AEs marked with * will be listed in the aCSR as per sponsor decision.

- Pre-treatment AEs
- All TEAEs*
- All TESAEs*
- All TEAEs related to OBI-999*
- TEAEs leading to death (with Grade 5 or “Fatal” as an outcome)*
- All TEAEs leading to discontinuation of OBI-999*
- All TEAEs leading to study discontinuation
- Post-treatment AEs

Number and percentage of patients with laboratory abnormalities with grade ≥ 3 will be provided by study part, by cohort (by dose level in Part A and by cancer type in Part B) and by visit.

B. Dose-limiting toxicities (DLTs) with OBI-999*

A DLT is defined as the occurrence of any of the following events, within the first cycle of treatment that is considered to be at least possibly related to OBI-999:

- Grade 4 neutropenia lasting more than 7 days.
- Febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia with ≥ Grade 2 bleeding requiring platelet transfusions.
- ≥ Grade 3 fatigue, nausea and vomiting or diarrhea for more than 72 hours despite optimal supportive care.
- Any Grade 4 gastrointestinal toxicity.
- Any ≥ Grade 3 non-hematological toxicity (except Grade 3 fatigue, nausea, vomiting, or diarrhea lasting < 24 hours with optimal therapy, Grade 3 non-hematologic laboratory abnormalities that resolve to Grade 1 or baseline within 14 days).

All TEAEs, unless they are determined to be not related to study drug will be taken into consideration in determining DLTs. The period for DLT observation is 21 days from the start of first dose of OBI-999 (i.e., Day 1).

DLTs (not to be programmatically derived; will be analyzed as collected on eCRF) will be displayed by dose level in a frequency table in decreasing order of incidence. AEs will be graded according to the NCI CTCAE V5.0. All TEAEs unless they have been determined to be not related to study drug will be DLTs and will be summarized by dose, SOC and PT. A listing of DLTs will be prepared.

C. MTD and RP2D of OBI-999

At the time of this version of the SAP, Part A (Dose-Escalation) was completed. The RP2D of 1.2 mg/kg was identified during SRC review.

PART B (COHORT-EXPANSION)

A. Objective Response*

Overall tumor response (not to be programmatically derived; will be analyzed as collected on eCRF) will be listed by cancer type and visit. For each patient, best overall response (BOR) is defined as the best overall tumor response (complete response [CR], partial response [PR)] stable disease [SD], and progressive disease [PD], or not evaluable [NE]) from the start of treatment until disease progression, recurrence or end of study. In general, the patient's best response assignment will depend on both the tumor measurement and confirmation criteria.

If an NE response is determined at a time point, this response will be ignored and subsequent non-NE responses will be used for the confirmation. For example, the sequence of tumor assessments: PR, NE, NE, CR, SD, that had more than two consecutive NEs, 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 criteria for confirmation of the response are 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 for all subsequent time points	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 for all subsequent time points	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.

Objective Response Rate (ORR) is defined as the percentage of patients with confirmed PR or CR based on tumor assessment as determined by RECIST 1.1 among all the patients in the safety and efficacy populations. A confirmed response will be defined as two or more consecutive assessments separated by at least 3 weeks. For summaries in the safety population, patients who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders and retained in the denominator. A summary with the number of patients by BOR categories, ORR and the Clopper-Pearson 95% confidence interval (CI) for the ORR will be provided.

A by-patient swim lane plot of time (weeks) to Overall Response will be provided, along with waterfall plots (bar plot) showing the best reduction in target lesion therapy will be presented for Cohort-Expansion patients.

Sample code for ORR is provided below:

```
proc freq data=data;
by cohort;
tables AVAL/binomial alpha=0.05 nocum norow;
exact binomial;
run;
```

If the BOR used for ORR based on unconfirmed and confirmed overall responses differs by 10%, then we will present the same summary for ORR based on unconfirmed overall responses as a sensitivity analysis.

B. Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the percentage of patients with confirmed CR, PR, or SD among all the patients of the safety and efficacy populations. A confirmed response will be defined as two or more consecutive assessments separated by at least 3 weeks. Patients who discontinue prior to post-baseline tumor assessments will be considered as non-responders and retained in the denominator. This analysis is similar to ORR.

If the BOR used for CBR based on unconfirmed and confirmed overall responses differs by 10%, then we will present the same summary for CBR based on unconfirmed overall responses as a sensitivity analysis.

C. Duration of Response

DOR is defined as the time from date of confirmed PR or CR to date of progression or death due to any cause and will be expressed in months. For patients who are alive and progression-free at the time of analysis, DOR will be censored at the last tumor assessment date. The DOR will only be evaluated for the subgroup of patients with a confirmed PR/CR using the Kaplan Meier method.

A summary of the patients with disease progression, or death, or the number of patients censored will be presented by the median time, Q1, Q3 and survival rates along with 95% CI, minimum and maximum will be provided.

Patients who discontinue from the study without experiencing any pre-defined events or patients who completed the study period without experiencing any pre-defined events will be included in statistical analysis as censored.

Sample code for duration of response is provided below:

```
ods output Quartiles=QUARTS;
proc lifetest data=DATA method=km OUTSURV=KMEST;
by COHORT;
time AVAL*CENSOR(1);
run;
ods output close;
```

D. Progression Free Survival

PFS is defined as the time from first dose of study drug until radiographically determined disease progression or death due to any cause, whichever occurs first. Patients who are still alive or who have no progressive disease reported at analysis will be censored at the last evaluable tumor assessment date.

Patients who discontinue from the study without experiencing any pre-defined events or patients who completed the study period without experiencing any pre-defined events will be included in

the statistical analysis as censored.

A summary of the patients with progression, or death, or the number of patients censored, presenting the median time, Q1, Q3 and survival rates along with 95% CI, minimum and maximum will be provided.

DOR and PFS summaries will be presented for safety and efficacy populations.

As additional analysis, ORR, CBR, DOR and PFS will be summarized for patients from Part A for safety and efficacy populations.

E. Percentage of patients with anti-OBI-999 antibodies (ADAs) in blood*

The number and percentage of patients with final ADA results in the blood will be summarized. ADAs titers over time will be summarized by cancer type in Part B using descriptive statistics, including percent coefficient of variation (CV%), geometric mean, and geometric SD using safety, and PK populations. Data listings will be produced for all ADA data.

10.7.2 Secondary Endpoints

PART A (DOSE-ESCALATION)

A. PK parameters of OBI-999 and its active metabolite MMAE.

PK analyses will be conducted by OBI Pharma, Inc. Please refer to the SAP developed by OBI for PK parameters (Appendix III).

PART B (COHORT-EXPANSION)

A. TEAEs/TESAEs and laboratory abnormalities as graded by NCI CTCAE version 5.0*.

Please refer to the analysis presented to Section 9.7.1.

B. PK parameters of OBI-999 and its active metabolite MMAE.

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

10.7.3 Exploratory Endpoints

A. Potential predictive biomarkers for OBI-999 activity such as expression of Globo H and other tumor-associated glycans or tumor molecular phenotypes.

The above analysis 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 Clinical Study Report (CSR).

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 9.7.

All safety endpoints will be analyzed using the safety population.

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

10.8.1 Exposure to Study Treatment and Treatment Compliance

The number of doses received, number of doses adjusted along with reasons of dose adjustment, total actual dose received in mg, total planned dose in mg, percentage of compliance (defined below), number of infusions interrupted along with reasons for infusion interruptions; number of infusions prematurely discontinued along with reasons for infusion prematurely discontinued, and the extent of exposure (calculated as last dose date – first dose date +1), will be summarized using descriptive statistics by study part, cohort, and overall.

Percentage of compliance for a patient will be defined as the total actual dose received divided by the total planned dose multiplied by 100.

$$Percentage\ of\ compliance\ (\%) = \frac{Total\ actual\ dose\ received\ in\ mg}{Total\ planned\ dose\ in\ mg}\ x\ 100$$

Extent of exposure will also be summarized categorically by number and percentages for each of the following categories and cumulatively according to these categories:

- > 0 and ≤ 3 weeks
- > 3 and ≤ 6 weeks
- > 9 and ≤ 12 weeks
- > 12 and ≤ 18 weeks
- > 18 and ≤ 24 weeks
- > 24 and ≤ 36 weeks
- > 36 and ≤ 48 weeks
- > 48 weeks

In addition, the percentages of compliance will be presented by the specific ranges for each study part and cohort:

- < 80%
- ≥ 80% to < 120%
- ≥ 120%

Data listings will be produced for all study drug administration data.

10.8.2 Laboratory Data

Baseline results, worst post baseline values (minimum or maximum value as determined by the specific analyte), change from baseline to worst post baseline values for hematology and serum chemistry collected by local laboratories, will be summarized using descriptive statistics, by study part, cohort and overall, in the safety population. Hematology will include Hemoglobin, Hematocrit,

, Platelet count, and White blood cell count with differential. Serum chemistry will include Albumin, Alanine aminotransferase, Alkaline phosphatase, Aspartate aminotransferase, Blood urea nitrogen or Urea, Bicarbonate, Creatinine, Creatine kinase, Electrolytes (Na, K, Cl, Ca, P, Mg), Glucose, Lactate dehydrogenase, Total bilirubin, Total protein, and Uric acid.

Results of coagulation tests (prothrombin time, international normalized ratio, activated partial thromboplastin time), urine analysis data will be summarized at each scheduled visit. Actual laboratory values, and changes from baseline in laboratory values, will be summarized in SI units using descriptive statistics, by study part, dose group, cohort and overall, in the safety population.

For coagulation tests, descriptive statistics will include CV%, geometric mean and geometric SD, calculated as: geometric SD = exp (SQRT(v)) where v is the squared standard deviation of the log-transformed values.

Shift tables classified by CTCAE grades (grade 0, grade 1, grade 2, grade 3, grade 4, grade 5) from baseline to worst post-baseline grade per cohort, may be presented by selected laboratory tests, where applicable. For laboratory tests for which grades of severity are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Urinalysis and microscopic analysis of the urine will be presented in a listing.

For laboratory results reported with a prefix, i.e., “<”, “<=”, “=>” or “>”, the value derived from reported results without a prefix will be analyzed.

Change from baseline scatter plot for selected laboratory analytes will be provided.

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

10.8.3 Vital Signs

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

Baseline results, change from baseline results of vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats per minute]), temperature [degree C]) signs will be summarized by study part, by cohort (by dose level in Part A and by cancer type in Part B) using descriptive statistics.

In addition, number and percentages of patients by categories (abnormal low, normal, abnormal high) by visit and overall will be calculated and summarized for each of Part A and Part B.

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

10.8.4 Electrocardiogram

ECG results will be summarized by study part, by cohort (by dose level in Part A and by cancer type in Part B) and scheduled visit. QTc interval in msec (Fredericia) will be summarized using descriptive statistics and ECG interpretation will be summarized by number and percentage.

ECG interpretation will be tabulated by a shift table (baseline vs. worst post baseline observation including unscheduled visits).

QTcF will be categorized using the FDA guidance thresholds as follows: > 450 msec, > 480 msec and > 500 msec. Frequency and proportion of patients that exceed the FDA guidance thresholds will be summarized by visit and overall, for Part A and Part B. Frequency and proportion of patients with increase from baseline of more than 30 msec and more than 60 msec will be summarized by visit and overall for Part A and Part B.

10.8.5 Other Safety Parameters

ECOG categories will be tabulated by visit and a shift table (baseline vs. worst post baseline observation including unscheduled visits).

Physical examination results (normal/abnormal-not clinically significant/abnormal-clinically significant/not evaluable/not done) will be listed and a shift table (baseline vs. worst post baseline observation, including unscheduled visits) will be displayed for each body system.

Ophthalmological examination categories will be listed by study part, by cohort (by dose level in Part A and by cancer type in Part B) and scheduled visit.

11. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

In the section §14.2 of the protocol the safety population is defined as all enrolled patients who receive at least 1 dose of study drug. The population used for analysis of clinical activity is defined as all enrolled patients who received at least one dose of study drug and had at least one follow-up tumor assessment scan, but it was not clearly stated this is the efficacy population. We clearly defined it in section §8 of the SAP.

The DOR is defined in section 14.3 of the protocol as the time from date of confirmed PR or CR to date of progression, but as we are applying a censoring rule to patients who are alive at the time of the analysis, we updated the definition in section 9.7.1 of the SAP to time from date of confirmed PR or CR to date of progression or death (from any cause).

OBI-999 2.0 mg/kg was planned to be administered in Part A but this dose was not administered to any subjects in Part A due to the toxicity observed with the 1.6 mg/kg dose. For this reason, this cohort will not be presented.

Efficacy endpoints will be analyzed in the safety and efficacy populations, because the definition of the efficacy population specifies that patients must have at least one follow-up assessment scan and so is closer to a per protocol population.

DLTs will not be derived and will be presented as collected on the eCRF. The following DLTs have been updated:

- “≥ Grade 3 fatigue, nausea and vomiting or diarrhea that does not resolve to Grade 1 or Baseline within 72 hours despite optimal supportive care” has been revised to “≥ Grade 3 fatigue, nausea and vomiting or diarrhea for more than 72 hours despite optimal supportive care”.
- “Any other Grade 3 or Grade 4 non-hematological toxicity (except Grade 3 fatigue, nausea, vomiting, or diarrhea lasting < 24 hours with optimal therapy, Grade 3 non-hematologic laboratory abnormalities that resolve to Grade 1 or baseline within 14 days)” has been

revised to. Any ≥ Grade 3 non-hematological toxicity (except Grade 3 fatigue, nausea, vomiting, or diarrhea lasting < 24 hours with optimal therapy, Grade 3 non-hematologic laboratory abnormalities that resolve to Grade 1 or baseline within 14 days)".

On 10 November 2023, Sponsor stated they stop the OBI-999-001 study and elected to generate an aCSR. Therefore, as per sponsor decision, the planned analyses have been changed to:

- In section §10.5, the protocol deviations will neither be summarized nor listed.
- In section §10.6.1, the baseline and demographic characteristics will be summarized using only the safety population and listed.
- In section §10.6.2, the medical history and current medical conditions will neither be summarized nor listed.
- In section §10.6.3, the prior and concomitant medications will neither be summarized nor listed.
- In section §10.6.4, the cancer history will be summarized using only the safety population and listed.
- In section §10.6.5, other medical history will not be listed.
- In section §10.6.6, prior cancer surgeries will neither be summarized nor listed.
- In section §10.6.7, prior cancer radiotherapy will neither be summarized nor listed.
- In section §10.6.8, prior cancer medication therapy will neither be summarized nor listed.
- In section §10.6.9, smoking history will neither be summarized nor listed.
- In section §10.7.1, adverse events that will be analyzed and listed have been marked with asterisks. Only ORR analysis using safety population and ADA analysis using safety and PK populations have been selected as CBR, DOR and PFS analyses will no longer be conducted for the aCSR. Only waterfall plot (bar plot) showing the best reduction in target lesion therapy will be presented for Cohort-Expansion patients.
- In section §10.8.1, only extent of exposure will be summarized, and all study drug administration data will be listed.
- In section §10.8.2, laboratory data will only be listed. OBI decided not to conduct normalization of local laboratory assessments; therefore, data will be listed as recorded.
- In section §10.8.3, vital signs data will only be listed.
- In section §10.8.4, electrocardiogram data will only be listed.
- In section §10.8.5, ECOG, physical examination and ophthalmological data will neither be summarized nor listed.

12. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all other edges.

In the top left portion of each table/listing, the sponsor's name, *protocol number, type of analysis (Draft or Final)* will be presented. In the top right portion of each table/listing, page X of Y will be presented. On the next line, a *table/listing number* followed by the *title* of the table/listing and

p*opulation* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name, Source Data, Extract date and Cut-off date* will appear bottom left in a string of each table/listing. The *date and time of creation* of table/listing will appear bottom left under to the SAS program name line.

Times New Roman, proportional 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002.

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

13. 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.

14. 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.

15. APPENDIX I. SCHEDULE OF ASSESSMENTS

TABLE 14-1 SCHEDULE OF ASSESSMENTS

Study Procedure	**Screening Visit**	**Treatment Period**							**EoS / ET**	**F/U**
Cycle (C) #	-	**Cycle 1**						**Cycle 2-35**		
Cycle # and Day		C1D1	C1D2	C1D4	C1D8	C1D11	C1D15	D1		
Window period (days)	-28 to -1	-1*	±1	±3	±3	±3	±3	±3	±7	
Informed consent[a]	X									
Demographics	X									
Eligibility screening	X	X								
Medical history[b]	X	X								
Physical examination[c]	X	X			X*			X	X	X
Height, weight[d]	X[d]	X						X	X	
Vital signs[e]	X	X						X	X	
Ophthalmology examination[f]	X							Q6wk for the first 6 months, then Q9wk thereafter[f]	X	
ECOG[g]	X							X	X	
12-lead ECG[h]	X	X		X[g]					X	
Pregnancy testing[i]	X								X	
Tumor biopsy[i]	X									
Hematology and serum chemistry[k]	X	X			X		X	Every week for Cycles 2 and 3, then D1 of Cycles 4+	X	
Coagulation and urinalysis[l]	X							D1 of each 21-day cycle[l]	X	
Drug administration[m]		X						D1 of each 21-day cycle		
Pharmacokinetic			See footnote n							

sample[n]										
Immunogenicity (ADA)[o]		X						See footnote o	X	X^n
Radiology evaluations (CT or MRI)[p]	X							Q6wk for the first 3 months, then Q9wk thereafter	X	
Concomitant medications	←									→
Adverse events		←								→

Abbreviations: ADA = anti-drug antibody; D = Day; C = Cycle; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoS = End of Study; ET = Early Termination; F/U = follow-up; MRI = magnetic resonance imaging; Q6wk = every 6 weeks; Q9wk = every 9 weeks

EoS Visit is the safety follow-up visit, conducted 28±7 days after the last OBI-999 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-999 administration.

Footnotes:

a. Informed consent to be obtained before any other study procedures are performed.

b. Medical history, including previous cancer therapies, cancer history, and past and ongoing concomitant illnesses which are relevant to the disease under study.

c. A complete physical examination is required at screening and end of study/early termination. Directed physical examinations may be limited to problem focused review of symptoms and major organ systems. This should include an assessment for signs and symptoms of peripheral neuropathy as this is a known adverse event associated with MMAE-based ADCs and may be expected to occur with OBI-999.

d. Height to be obtained at screening only.

e. Vital signs include temperature, blood pressure and pulse. Temperature measurement will be obtained as clinically indicated.

f. Performed by ophthalmologist as follows:
   a. Part A - At screening, every 2 cycles for the first 6 months (C2, C4, C6, C8), then every 3 cycles thereafter (C11, C14 and so on), and the end of study/early termination visit.
   b. Part B – At screening and at the discretion of the Investigator during the course of the study.

g. ECOG performance status: at screening, D1 of each cycle, and end of study/early termination

h. 12-lead ECG with assessment of QTcF: at screening, Cycle 1 Day 1, Cycle 1 Day 3 (48± 2 hours after the end of the Cycle 1 Day 1 OBI-999 infusion) and EoS/ET. The ECG testing on C1D4 could be tested 24 hours before but no later than C1D4.

i. 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

j. Tumor biopsy samples are mandatory at screening visit. Fresh (preferred) tissue or archival tissue is acceptable. A minimum of 5 slides are required for the central laboratory Globo H assay for determination of eligibility in Part B. Up to 10 unstained additional slides should be provided, depending on availability, for the protocol defined exploratory studies.

k. Hematology and Serum chemistry (Laboratory Assessments: Protocol Table 12-1). Blood draw is prior to OBI-999 infusion. For C2D1 and each cycle after, laboratory assessments may be drawn 72 hours in an advance of infusion.

   Hematology: hematocrit, hemoglobin, erythrocyte count, white blood count, absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count.
   Serum chemistry: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatine kinase, lactate dehydrogenase, total bilirubin, and uric acid. Creatinine clearance will be calculated by Cockcroft Gault equation at screen visit, week 1 and EoS/ET.

l. Coagulation, and Urinalysis (Laboratory Assessments: Protocol Table 12-1). Blood draw and urine collection is prior to OBI-999 infusion. Only urinalysis will be collected at Day 1 of Cycles 2-35.

   Coagulation: prothrombin time, activated partial thromboplastin time, and international normalized ratio.
   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

m. OBI-999 is given on Day 1 of each 21-day cycle until DLT, disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurs earlier.

n. Pharmacokinetic: (for analysis of serum concentration of OBI-999 total antibody, ADC and free MMAE). Detailed sampling schedule in Table 14.2 (Part A) and Table 14.3 (Part B).

o. Immunogenicity studies (ADA) - ADA samples will be collected. Detailed sampling schedule in Table 14.2 (Part A) and Table 14.3 (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.

p. Radiology (CT or MRI scan) evaluations of tumor response: Performed during screening and during the study every 6 weeks for the first 3 months, and then every 9 weeks until discontinuation of study treatment, disease progression, death, or initiation of further systemic cancer therapy, including radiation therapy, whichever occurs earlier. CT or MRI scan will be performed within 1 week prior to the start of the next cycle. Unscheduled scan can be performed anytime, if needed to confirm disease progression. Radiology assessment for early

termination/end of study, should ONLY be performed if ≥9 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 AND ADA SAMPLING SCHEDULE

Cycle	Cycle 1 and Cycle 2						Cycle 3 and Cycle 4		Cycle 5-8, 12 and every 4 cycles thereafter	EoS / ET
Cycle Day	**D1**	**D2**	**D4**	**D8**	**D11**	**D15**	**D1**	**D8**	**D1**	**±7 days**
Pharmacokinetic Samples										
Before infusion	X[a]						X[b]		X[b]	
30 minutes after end of infusion (90 min)[c]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X	X[d]	X	X
2 hours after end of infusion (180 min)[c,e]	X									
4 hours after end of infusion (300 min)[c,e]	X									
8 hours after end of infusion (540 min)[c,e]	X									
Immunogenicity Studies (ADA)[f]	X						X		X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EoS = End of Study; ET = Early Termination; min = minute

OBI-999 infusion should be administered on Day 1of every 21-day cycle throughout the study treatment period.

The infusion duration of Cycle 1 and Cycle 2 are 60 ± 10 minutes and can be reduced to 30 ± 10 minutes from Cycle 3, if there were no infusion related adverse events on prior infusions and at the discretion of the Investigator.

a. Cycle 1 Day 1 (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 on D1 can be collected in a window of ±15 minutes.
d. Samples on Days 2, 4, 8, 11, and 15 can be collected in a window of ±2 hours based on the end of infusion on Day 1.

e. If there is change of the infusion rate or interruption of infusion, the PK sampling on Day 1 is to be collected from the exact time of completion of infusion to obtain the post-infusion samples after the end of infusion. Exact time of sample collection and the reason for interruption should be documented in the eCRF.
f. ADA samples will be collected along with pre-infusion PK samples. No post-infusion ADA samples will be collected. For subjects with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.

TABLE 14-1 PART B - PHARMACOKINETIC AND ADA SAMPLING SCHEDULE

Cycle	Cycle 1 and Cycle 2					Cycle 3, Cycle 4, Cycle 8, and Every 4 Cycles Thereafter	EoS / ET
Cycle Day	**D1**	**D2**	**D4**	**D8**	**D15**	**D1**	**±7 days**
Pharmacokinetic Samples							
Before infusion	X[a]					X[b]	
30 minutes after end of infusion (90 min)[c]	X	X[d,g]	X[d,g]	X[d]	X[d]	X	X
6 hours after end of infusion (420 min)[c,e]	X						
Immunogenicity Studies (ADA)[f]	X					X	X

Abbreviations: ADA = anti-drug antibody; C = Cycle; D = Day; EoS = End of Study; ET = Early Termination; min = minute
OBI-999 infusion should be administered on Day 1of every 21-day cycle throughout the study treatment period.
The infusion duration of Cycle 1 and Cycle 2 are 60 ± 10 minutes, and can be reduced to 30 ± 10 minutes from Cycle 3, if there were no infusion related adverse events on prior infusions and at the discretion of the Investigator.

a. Cycle 1 Day 1 (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 on D1 can be collected in a window of ±15 minutes.
d. Samples on Days 2, 4, 8, and 15 can be collected in a window of ±2 hours based on the end of infusion on Day 1.
e. If there is change of the infusion rate or interruption of infusion, the PK sampling on Day 1 are to be collected from the exact time of completion of infusion to obtain the post-infusion samples after the end of infusion. Exact time of sample collection and the reason for interruption should be documented in the eCRF.
f. ADA samples will be collected along with pre-infusion PK samples. No post-infusion ADA samples will be collected. For subjects with persistent antibodies at end of study, an additional ADA sample will be collected at 4 months after the end of study visit.
g. This intensive PK sampling will be collected from first 5 patients in each cohort.

16. 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

17. APPENDIX III PHARMACOKINETIC ANALYSIS PLAN

Pharmacokinetic Analysis Plan

A Phase 1/2, Open-Label, Dose-Escalation and Cohort-Expansion Study Evaluating the Safety, Pharmacokinetics, and Therapeutic Activity of OBI-999 in Patients With Advanced Solid Tumors

Version 1.0

DATE: 30 NOV 2021

PHARMACOKINETIC ANALYSIS PLAN SIGNATURE PAGE

Pharmacokinetic Analysis Plan V1.0 (Dated 30NOV 2021) for Protocol OBI-999-001.

	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			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
$AUC_{(0\text{-last})}$	AUC to the Last Measurable Concentration
$AUC_{(0\text{-t})}$	AUC from 0 to time t
$AUC_{(0\text{-}\infty)}$	AUC Extrapolated to Infinity
ADC	Antibody drug conjugate
BMI	Body Mass Index
BQL	Below the Quantification Limit
C_{last}	Last Measurable Concentration (above the quantification limit)
CL	Clearance
cm	Centimeter(s)
C_{max}	Maximum Serum Concentration
CSR	Clinical Study Report
CV	Coefficient of Variation
ECL	Electrochemiluminescence
EDC	Electronic Data Capture
g	Gram(s)
GM	Geometric Mean
GSD	Geometric Standard Deviation
h	Hour(s)
K_e	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)
MMAE	monomethyl auristatin E
NCA	Noncompartmental Analysis
µg	Microgram(s)
PK	Pharmacokinetic(s)
SD	Standard Deviation
$t_{1/2}$	Apparent Terminal Elimination Half-Life
T_{last}	Time of Last Measurable Concentration
T_{max}	Time to Maximum Serum Concentration (C_{max})
V_z	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-999-001]. This document is based on protocol, version 7.0, dated 21 July 2021.

This document reiterates key PK elements in the study design of Protocol OBI-999-001and 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-999 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-999, an antibody drug conjugate (ADC), targeting Globo H in patients with locally advanced or metastatic solid tumors. Part A is designed to establish the MTD and RP2D of OBI-999. Part B is intended to further characterize the safety and clinical activity profile of the RP2D dose of OBI-999 administered as monotherapy in patients with advanced solid tumors.

2.2. Dose Administration

OBI-999 were administered as a 60-minute intravenous (IV) infusion on Days 1of each 21-day cycle for the initial 2 cycles (Cycle 1 and Cycle 2). The infusion duration for Cycles 3 and beyond may be reduced, at the Investigator's discretion, to 30 minutes if no infusion related AEs occur during the first 2 cycles. For Part A (Dose-Escalation), OBI-999 was planned to be given at doses of 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg (capping calculations at a maximum of 100 kg) using a 3+3 design to identify the MTD and RP2D. For Part B (Cohort-Expansion), OBI-999 will be given at the RP2D of 1.2 mg/kg (capping administered dose to a maximum of 120 mg for 100 kg)

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 0.5 (±15 min), 2 (±15 min), 4 (±15 min), 8 (±15 min), 24 (± 2 h, on Day2), 72 (±2 h, on Day4),

168 (±2 h, on Day8), 240 (±2 h, on Day11) and 336 hours (±2 h, on Day15) after the end of the infusion.

2.4. Analytical Methods

As OBI-999 is an antibody drug conjugate (ADC) and composed of a humanized monoclonal lgG1antibody conjugated with monomethyl auristatin E (MMAE, vedotin) targeting Globo H. The concentration of OBI-999 and total antibody in the serum samples were determined using a validated electrochemiluminescence (ECL) method with assay ranges of 15 to 24000 ng/mL and 100 to 15000 ng/mL, respectively. The concentration of MMAE in the serum samples were determined using a validated LC/MS/MS method with an assay range of 2 to 4000 pg/mL.

3. PHARMACOKINETIC AN ALYSIS 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

• Serum 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

Serum concentrations will be listed by subject (PK Listing 4-6), 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. Serum drug concentrations will also be summarized (PK Table 2-4) and plotted. PK Figure 1 to PK Figure 12 will plot all individual subject and mean serum 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 8.3 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 7-9).

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.

t½ (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 doses 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 4-6). PK estimates will be summarized in PK Table 5-7. 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	
Other or Unknown	

PK Table 2: Summary Statistics for Concentrations of OBI-999 by Nominal Time

Subject ID	OBI-999 Concentration (µg/mL) by Nominal Time[1] After Dose (h)									
	0	1.5	3	5	9	25	73	169	241	337
UXX-001	x	x	x	x	x	x	x	x	x	x
UXX-002	x	x	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	x	x	x	x
Statistics										
N_2	x	x	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	x.x	x.x
SD	x.x	x.x	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	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(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 Concentrations of total antibody by Nominal Time

Subject ID	Total Antibody Concentration (µg/mL) by Nominal Time[1] After Dose (h)									
	0	1.5	3	5	9	25	73	169	241	337
UXX-001	x	x	x	x	x	x	x	x	x	x
UXX-002	x	x	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	x	x	x	x
Statistics										
N_2	x	x	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	x.x	x.x
SD	x.x	x.x	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	x.x	x.x
(Min, Max)	(x, x)	(x, x)	(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 4: Summary Statistics for Concentrations of MMAE by Nominal Time

Subject ID	MMAE (ng/mL) by Nominal Time[1] After Dose (h)									
	0	1.5	3	5	9	25	73	169	241	337
UXX-001	x	x	x	x	x	x	x	x	x	x
UXX-002	x	x	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	x	x	x	x
Statistics										
N_2	x	x	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	x.x	x.x
SD	x.x	x.x	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	x.x	x.x
(Min, Max)	(x, x)	(x,	(x,	(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 5: Summary Statistics for PK Parameters of OBI-999

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)	$t_{1/2}$ (h)	Vss (L)
N								
Mean								
SD								
Min								
Median								
Max								
CV %								
GM								
GSD								

PK Table 6: Summary Statistics for PK Parameters of total antibody

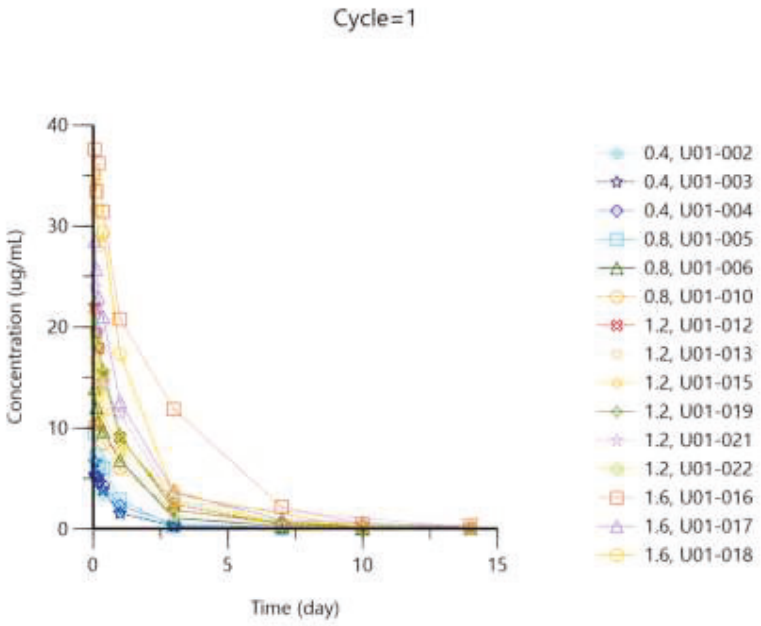
Statistic	T_{max} (h)	C_{max} (µg/mL)	C_{max_D} (µg/mL/mg)	$AUC_{(0\text{-}last)}$ (h×µg/mL)	$AUC_{(0\text{-}last)\_D}$ (h×µg/mL/mg)	CL (L/h)	$t_{1/2}$ (h)	Vss (L)
N								
Mean								
SD								
Min								
Median								
Max								
CV %								
GM								
GSD								

PK Table 7: Summary Statistics for PK Parameters of MMAE

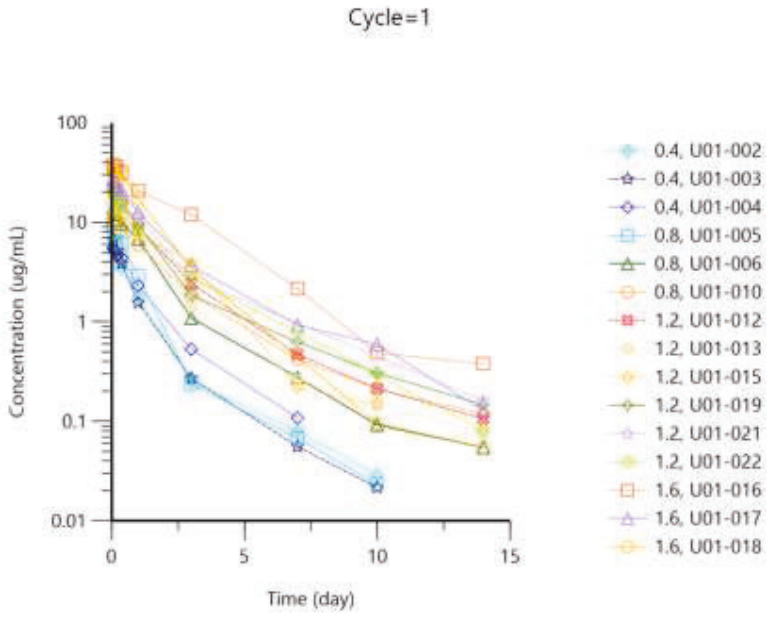
Statistic	T_{max} (h)	C_{max} (ng/mL)	C_{max_D} (ng/mL/mg)	$AUC_{(0\text{-}last)}$ (h×ng/mL)	$AUC_{(0\text{-}last)\_D}$ (h×ng/mL/mg)	$t_{1/2}$ (h)
N						
Mean						
SD						
Min						
Median						
Max						
CV %						
GM						
GSD						

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

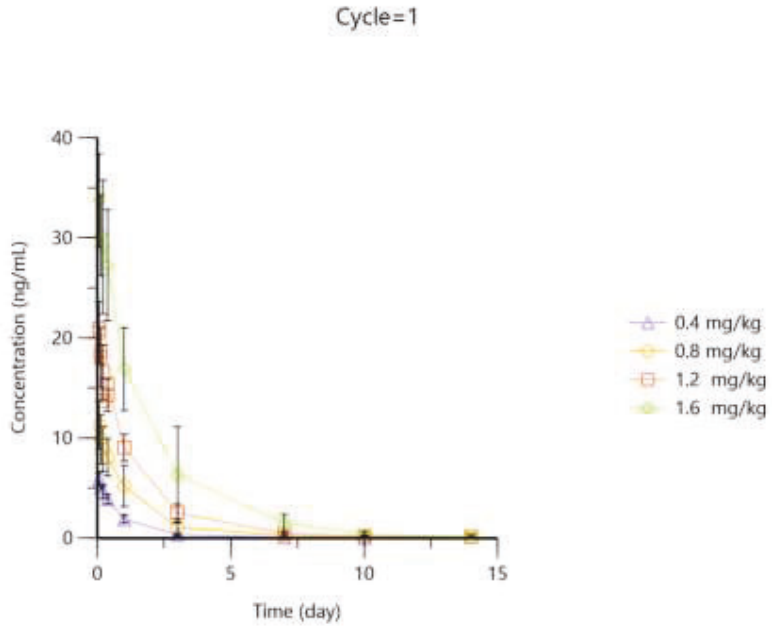
PK Figure 1: Concentration Profiles of OBI-999 for All Subjects by Time



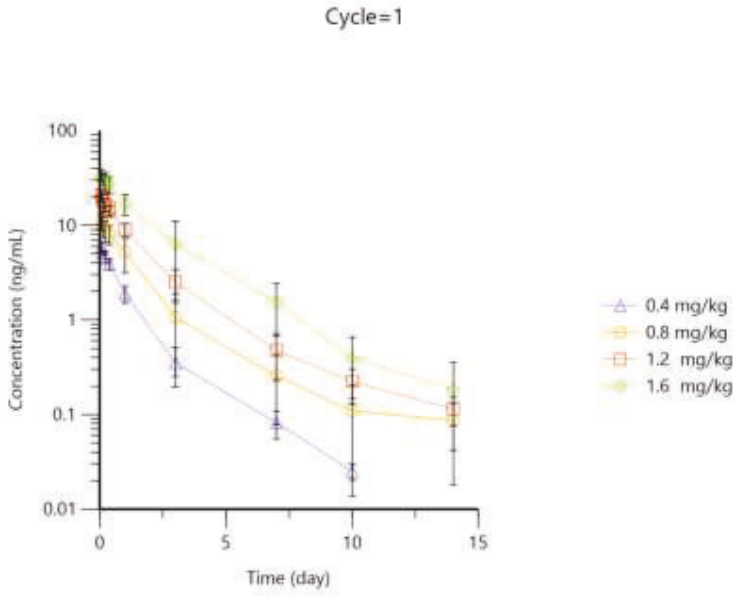
PK Figure 2: Semi-log Concentration Profiles of OBI-999 for All Subjects by Time



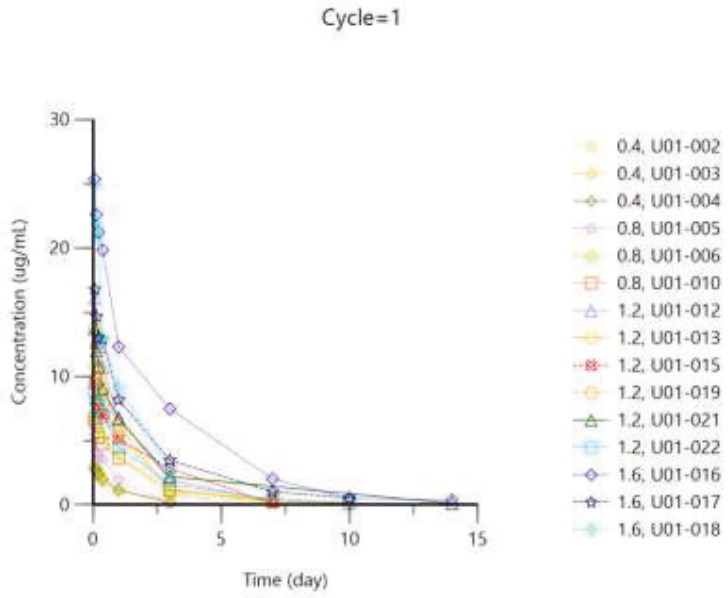
PK Figure 3: Mean Concentration of OBI-999 by Nominal Time



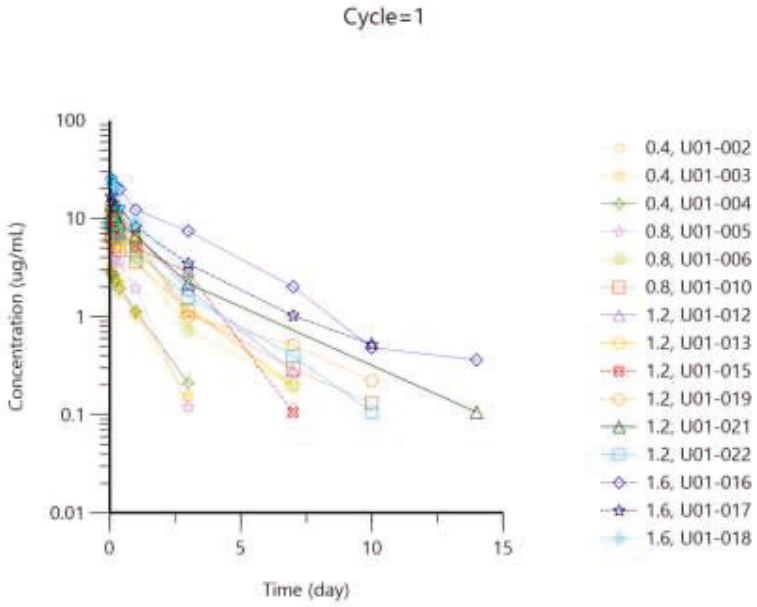
PK Figure 4: Mean Concentration of OBI-999 by Nominal Time (Semi-Log)



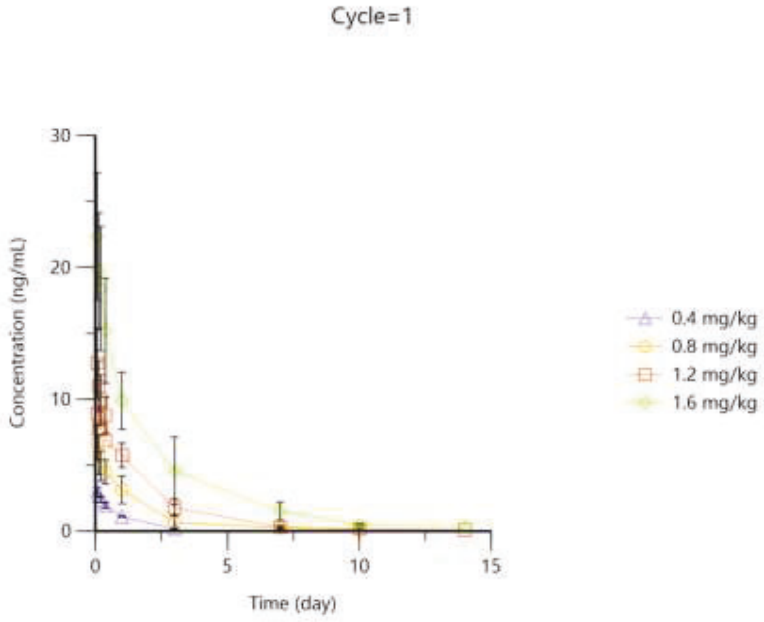
PK Figure 5: Concentration Profiles of total antibody for All Subjects by Time



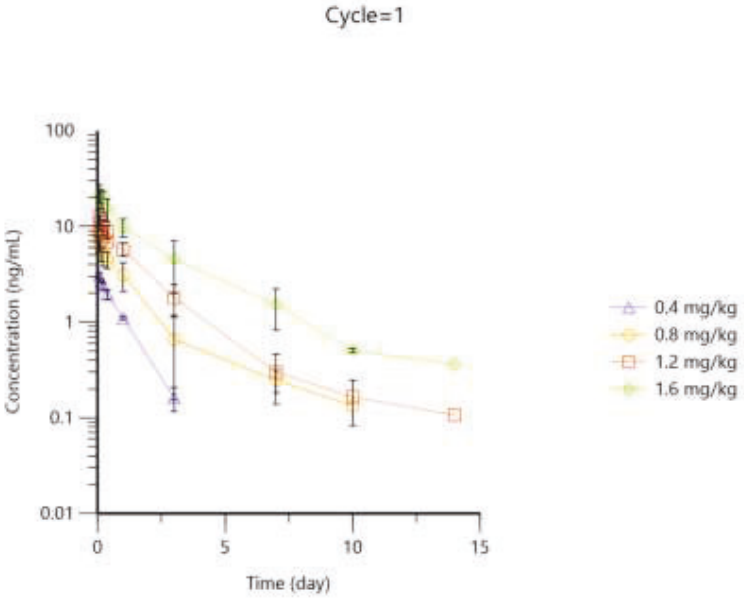
PK Figure 6: Semi-log Concentration Profiles of total antibody for All Subjects by Time



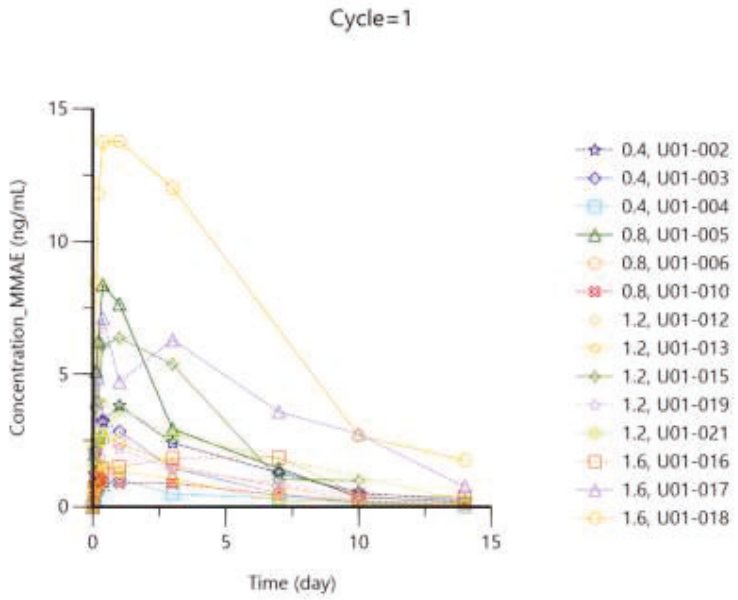
PK Figure 7: Mean Concentration of total antibody by Nominal Time



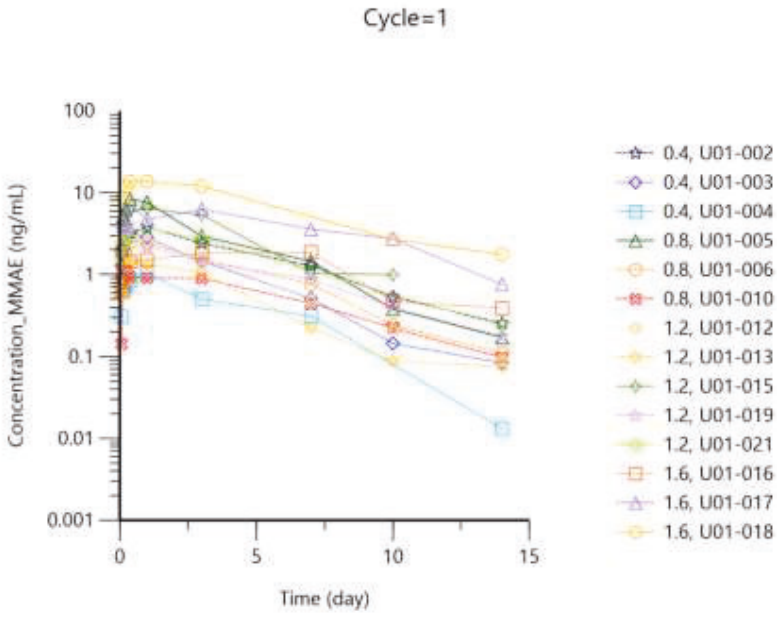
PK Figure 8: Mean Concentration of total antibody by Nominal Time (Semi-Log)



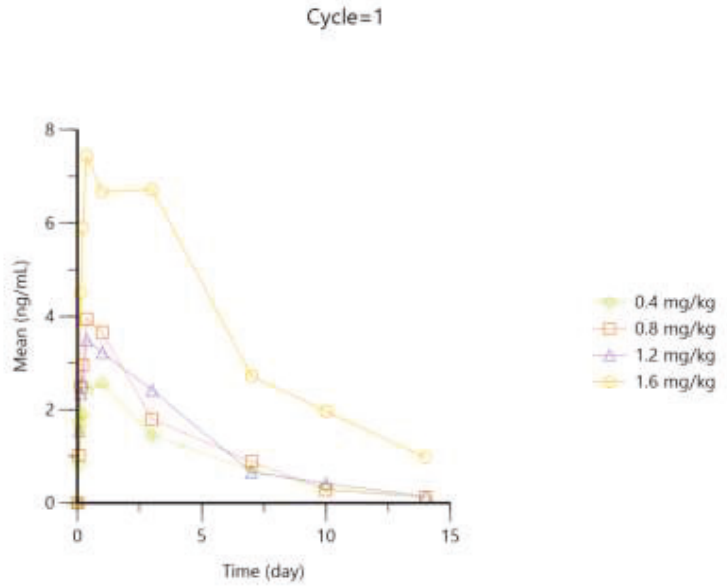
PK Figure 9: Concentration Profiles of MMAE for All Subjects by Time



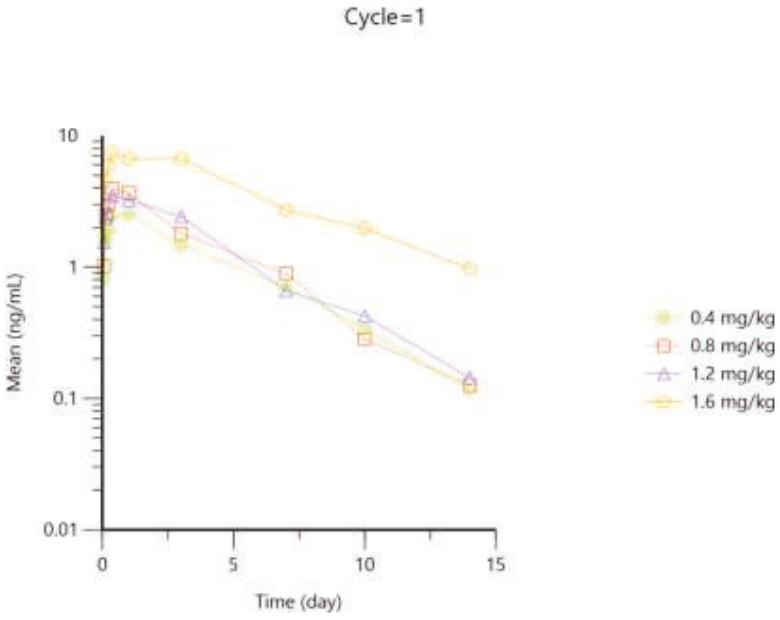
PK Figure 10: Semi-log Concentration Profiles of MMAE for All Subjects by Time



PK Figure 11: Mean Concentration of MMAE by Nominal Time



PK Figure 12: Mean Concentration of MMAE 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-999 Dosing

Subject ID	Dose (mg)	Date of Infusion	Start Time	End Time
UXX-001				
UXX-002				
UXX-003				

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	Deviat Categ
UXX-001										
UXX-002										
UXX-003										

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-999 Concentrations in Serum

Subject ID	Nominal Time[1] (h)	Actual Time[1] (h)	Lab Reported Drug Concentration (µg/mL)	Analysis Drug Concentration (µg/mL)	Used in K_e 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	
…							

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

PK Listing 5: Subject Level Total Antibody Concentrations in Serum

Subject ID	Nominal Time[1] (h)	Actual Time[1] (h)	Lab Reported Drug Concentration (µg/mL)	Analysis Drug Concentration (µg/mL)	Used in K_e 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	
…							

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

PK Listing 6: Subject Level MMAE Concentrations in Serum

Subject ID	Nominal Time[1] (h)	Actual Time[1] (h)	Lab Reported Drug Concentration (ng/mL)	Analysis Drug Concentration (ng/mL)	Used in K_e 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	
…							

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

PK Listing 7: Subject-Specific Pharmacokinetic Parameters for OBI-999

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									
…									

PK Listing 8: Subject-Specific Pharmacokinetic Parameters for total antibody

Subject	T_{max}	C_{max}	C_{max_D}	$AUC_{(0\text{-last})}$	$AUC_{(0\text{-last})\_D}$	CL	K_e	$t_{1/2}$	Vss

ID	(h)	(µg/mL)	(µg/mL/mg)	(h×µg/mL)	(h×µg/mL/mg)	(L/h)	(1/h)	(h)	(L)
UXX-001									
UXX-002									
UXX-003									
…									

PK Listing 9: Subject-Specific Pharmacokinetic Parameters for MMAE

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