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CLINICAL RESEARCH PROTOCOL

STUDY DRUG:	OBI-999 (a humanized Globo H monoclonal antibody drug conjugate)
STUDY NUMBER:	OBI-999-001
PROTOCOL 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
TRIAL REGISTRATION NUMBERS:	
ClinicalTrials.gov:	NTC04084366
US FDA IND Number:	143960
SPONSOR:	OBI Pharma, Inc. Room W1907, 19F, #3, YuanQu St. Nankang Software Park, Nangang District, Taipei City 115, Taiwan, R.O.C.
VERSION NUMBER:	Version 7.0

CONFIDENTIAL

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SPONSOR APPROVAL PAGE

[redacted] Date: 28 JUL 2021

PROTOCOL REVISION HISTORY

Version	Date	Comment
1.0	31 Jul 2019	Initial version
2.0	21 Aug 2019	a. Revised the dose level cohorts to evaluate 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg b. Revised the DLT definition c. Revised the eligibility criteria d. Added details regarding the monitoring and management of infusion reactions
3.0	26 Aug 2019	a. Revised to include long-term safety follow-up to monitor for the development of neuropathy b. Added stopping rules for excessive toxicity
4.0	12 Sep 2019	a. Removed Exclusion Criteria #4 and #5 to avoid redundancy b. Revised the storage conditions for diluted OBI-999 drug product to no more than 4 hours at 2-8°C or room temperature
5.0	16 Oct 2019	a. Added ophthalmic examinations b. Clarified the Safety Review Committee meeting frequency
6.0	27 Apr 2020	a. Removed circulating tumor cell assessments, objectives, and endpoints b. Updated Exclusion Criteria #1, #3, and #9 c. Revised the physical examination, hematology, serum chemistry, urinalysis, and radiology assessment frequency
7.0	21 Jul 2021	a. Updated the content to focus on Part B - Expansion Cohort b. Removed the gastric cancer and esophageal cancer cohorts from Part B c. Added that the Recommended Phase 2 Dose has been determined to be 1.2 mg/kg on Day 1 of a 21-day cycle d. Updated the assessment schedule for ophthalmology examinations in Part B

Version	Date	Comment
		e. Updated the tumor tissue sample guidelines f. Updated the pharmacokinetic and ADA sampling schedule for Part B g. Clarified that intensive PK sampling will be collected from the first 5 patients in each cohort only

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

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to OBI-999-011 are the confidential and proprietary information of OBI Pharma, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of OBI Pharma, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the in the Declaration of Helsinki, Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines and all applicable regulatory requirements. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by OBI Pharma, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about OBI-999 and the study.

Investigator's Signature	**Date**
Name (printed)	**Site**

1 Synopsis

Title of Study:	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
Phase of Development:	1/2
Rationale:	Globo H is a hexasaccharide glycosphingolipid located endogenously on the outer membrane of epithelial cells and was first identified in breast cancer cells. Globo H was found to be overexpressed on the cell surface of several epithelial cancers such as breast, pancreatic, ovarian, endometrial, gastric, lung, and prostate cancers. Globo H has been associated with tumor stem cells, as a potent inducer of angiogenesis and immune suppressor through Notch signaling, rendering it a target for cancer therapy. OBI-999 is an antibody drug conjugate (ADC) composed of a human recombinant immunoglobulin G (IgG) monoclonal antibody that selectively and specifically binds to Globo H, attached by a linker to the antimitotic agent monomethyl auristatin E (MMAE). The mechanism of action of OBI-999 is based on tumor-selective delivery of MMAE to Globo H-expressing tumors with subsequent tumor cell death. Preclinical studies demonstrated that OBI-999 antibody binds specifically to Globo H antigen, and antitumor efficacy was noted in preclinical breast, gastric, pancreatic, and lung cancer tumor xenograft models.
Study Purpose:	This is a 2-part study: Part A (Dose-Escalation) is designed to establish the maximum tolerated dose (MTD) and Recommended Phase 2 dose (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.
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 MTD and RP2D of OBI-999. 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 MMAE. The exploratory objective is: • To explore potential predictive biomarkers of OBI-999 activity.
Study Design:	This is a Phase 1/2, open-label, dose-escalation, and cohort-expansion study of OBI-999, an ADC-targeting Globo H in patients with advanced solid tumors.
	<u>Part A – Dose-Escalation:</u> Up to 30 eligible patients with advanced solid tumors will be enrolled in Part A. No Globo H expression testing will be 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 calculations at a maximum of 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 as 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 events (AEs) will be 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. 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.

	Part B – Expansion Cohort: 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 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 type 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.
Selection of Patients – Inclusion Criteria:	Inclusion Criteria: Patients must meet all of the following criteria in order to be included in the study (for both Parts A and B unless specified otherwise): 1. Male or female patients, 18 years of age or older at the time of consent. 2. Provide written informed consent prior to performing any study-related procedure. 3. Histologically or cytologically confirmed patients with advanced solid tumors. 4. Patients must have been treated with established standard-of-care therapy, or physicians have determined that such established therapy is not sufficiently efficacious, or patients have declined to receive standard-of-care therapy. In the latter case, the informed consent must state the effective therapies the patient is declining. 5. Measurable disease (i.e., at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]). 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 7. Adequate organ function defined as: a. Hepatic:

	i. Serum alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN), ≤5 × ULN in the presence of liver metastases ii. Serum aspartate aminotransferase (AST) ≤3 × ULN, ≤5 × ULN in presence of liver metastases iii. Serum bilirubin ≤1.5 × ULN (unless due to Gilbert's syndrome or hemolysis) b. Renal: i. Creatinine clearance >50 mL/minute using Cockcroft Gault equation c. Hematologic: i. Absolute neutrophil count ≥1,500/μL ii. Platelets ≥100,000/μL iii. Hemoglobin ≥8 g/dL 8. Patient is willing and able to comply with all protocol-required assessments, visits, and procedures, including pretreatment tumor biopsy. Archival tumor biopsies are acceptable at baseline. 9. Females of childbearing potential must have negative serum pregnancy test prior to starting study therapy, and agree to use a reliable form of contraceptive during the study treatment period and for at least 120 days following the last dose of study drug. Patient not of childbearing potential (i.e., permanently sterilized, postmenopausal) can be included in study. Postmenopausal is defined as 12 months with no menses without an alternative medical cause. Male patients must agree to use an adequate method of contraception during the study treatment period and for at least 120 days following the last dose of study drug. 10. Cannot be breast feeding. 11. Patients with human immunodeficiency virus (HIV) infection are eligible if CD4+ T-cell counts ≥ 350 cells/μL; patients on anti-retroviral therapy (ART) should be on an established dose for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to enrollment. 12. Patients with serological evidence of chronic hepatitis B virus (HBV) infection are eligible if they have an HBV viral load below the limit of quantification with or without concurrent viral suppressive therapy. 13. Patients with a history of hepatitis C virus (HCV) infection should have completed curative antiviral treatment and have a viral load below the limit of quantification.

	14. Patients in Part B (Cohort-Expansion) – must have documented Globo H H-score ≥ 100 from a qualified laboratory IHC assay in one of the following tumor types to be enrolled in the respective cohort: • Cohort 1: Pancreatic cancer o Histopathologically confirmed patients with metastatic adenocarcinoma of the pancreas. • Cohort 2: Colorectal cancer o Histopathologically confirmed patients with metastatic colorectal adenocarcinoma. • Cohort 3: Basket (any solid tumor type other than those included in Cohorts 1 and 2). o Histologically or cytologically confirmed patients with advanced solid tumors.
Selection of Patients – Exclusion Criteria:	<u>Exclusion Criteria:</u> Patients meeting any of the following criteria are ineligible to participate in this study: 1. Less than 3 weeks from prior cytotoxic chemotherapy or radiation therapy; and less than 5 half-lives or 3 weeks, whichever is shorter, from prior biologic therapies, prior to the first dose of OBI-999. 2. Has undergone a major surgical procedure (as defined by the Investigator) or significant traumatic injury within 28 days prior to the first dose of OBI-999. 3. Sensory or motor neuropathy of Grade 2 or greater. 4. Patients with a history of solid organ transplant. 5. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Grade 0 or 1 (using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 5.0), except for alopecia and laboratory values listed in the inclusion criteria. 6. Receipt of any prior therapy targeting Globo H. 7. Known hypersensitivity to OBI-999 or its excipients. 8. Has known untreated central nervous system (CNS) metastases. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period. 9. Has significant clinical cardiac abnormality (e.g., clinical heart failure or unstable angina). 10. Any medical co-morbidity that is life-threatening or, in the opinion of the Investigator, renders the patient unsuitable for participation in a clinical trial due to possible noncompliance, would place the

	patient at an unacceptable risk and/or potential to affect interpretation of results of the study. 11. Is receiving any concurrent prohibited medication as listed in Section 8.6.3.
Planned Sample Size:	Up to 30 patients will be 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.
Dose/ Route/ Regimen for Investigational Therapy:	OBI-999 is an anti-Globo H ADC. OBI-999 drug product (in final concentration 5 mg/mL) will be supplied by OBI Pharma Inc. OBI-999 will be administered as a 60±10-minute IV infusion on Day 1 of each 21-day cycle. The infusion duration for Cycles 3 and beyond may be reduced, at the Investigator's discretion, to 30 minutes if the infusions in the first 2 cycles are well tolerated. • For Part A, 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) until the MTD and RP2D were determined. • For Part B, OBI-999 will be given at the RP2D of 1.2 mg/kg (capping calculations at a maximum of 100 kg).
Reference Therapy:	None
Treatment Duration:	The study 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. The safety follow-up visit will be conducted 28 days after the last dose of study treatment for both parts of the study.

Criteria for Evaluation:	Safety: Safety assessments will include incidence and severity of AEs and serious adverse events (SAEs), clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis), vital sign measurements, electrocardiograms (ECGs), ophthalmology, and physical examination. Physical examinations will include a targeted assessment for signs and symptoms of peripheral neuropathy. Safety assessments will be performed at screening and throughout the study. DLTs (Part A only): 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 that does not resolve to Grade 1 or Baseline within 72 hours despite optimal supportive care. • Grade 4 gastrointestinal toxicity. • 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). All AEs unless they are determined to be not related to study drug will be taken into consideration in determining DLTs. NCI CTCAE version 5.0 will be the basis for the descriptive terminology and grading of AEs. The period for DLT observation is 21 days from the start of first dose of OBI-999 (i.e., Day 1). Immunogenicity: Samples for evaluation of ADAs will be collected prior to infusion on Day 1 of Cycles 1-8, Cycle 12 and every 4 cycles thereafter. A single sample will be collected at the end of study or end of treatment visit. Pharmacokinetics: Samples for the evaluation of serum concentration of OBI-999 total antibody, ADC, and free MMAE will be collected as follows: Part A of the study: • Day 1 of Cycles 1 and 2 – prior to infusion, and 30 minutes, 2 hours, 4 hours, 8 hours after the end of infusion.

	• Days 2, 4, 8, 11 and 15 of Cycles 1 and 2 (ie, 24, 72, 168, 240 and 336 hours after the end of infusion). • Day 1 of Cycle 3 and Cycle 4 – prior to infusion and 30 minutes after the end of infusion. • Day 8 of Cycle 3 and Cycle 4 – 168 hours after the end of infusion. • Day 1 of Cycles 5-8, 12 and every 4 cycles – prior to infusion and 30 minutes after the end of infusion. • End of treatment visit – single sample. Part B of the study: • Day 1 of Cycles 1 and 2 – prior to infusion, and 30 minutes and 6 hours after the end of infusion. • Days 2 and 4 of Cycles 1 and 2 (ie, 24 and 72 hours after the end of infusion, this intensive PK sampling will be collected from first 5 patients in each cohort). • Day 8 and 15 of Cycles 1 and 2 (ie, 168 and 336 hours after the end of infusion). • Day 1 of Cycle 3, Cycle 4, Cycle 8, and every 4 cycles - prior to infusion and 30 minutes after the end of infusion. • End of treatment visit – single sample. Pharmacokinetic parameters will be calculated using a non-compartmental method from the PK samples collected during Cycles 1 and 2 and will include but will not be limited to maximum serum concentration (C_{max}), area under the concentration curve (AUC), elimination half-life ($t_{1/2}$), clearance (Cl), time to reach maximum concentration (T_{max}), and volume of distribution (V_d). <u>Preliminary Clinical Activity Profile</u>: Tumor response will be evaluated by the Investigator using RECIST 1.1. Tumor status assessment will be performed pretreatment (up to 28 days prior to dosing). During the study, tumor response will be assessed 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.
Study Endpoints:	<u>Part A – Dose-Escalation:</u> Primary endpoints: • AEs/SAEs and laboratory abnormalities as graded by NCI CTCAE version 5.0. • DLTs with OBI-999. • MTD and RP2D of OBI-999.

	Secondary endpoint: • PK parameters of OBI-999 and its active metabolite MMAE. Exploratory endpoint: • Potential predictive biomarkers for OBI-999 activity such as expression of Globo H and other tumor-associated glycans or tumor molecular phenotypes. <u>Part B – Expansion Cohort:</u> Primary endpoints: • Percentage of patients with objective rsponse, clinical benefit, DOR, and PFS according to RECIST 1.1. • Percentage of patients with ADAs in blood. Secondary endpoints: • AEs/SAEs and laboratory abnormalities as graded by NCI CTCAE version 5.0. • PK parameters of OBI-999 and its active metabolite MMAE. Exploratory endpoint: • Potential predictive biomarkers for OBI-999 activity such as expression of Globo H and other tumor-associated glycans or tumor molecular phenotypes.
Statistical Methods and Planned Analyses:	Analyses will be conducted by dose level in Part A and by cancer type in Part B. Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations, minimum and maximum values. Descriptive summaries of time to event data will include medians and confidence intervals. Graphical summaries of the data may be presented. All data will be listed for all patients. Further details of the analysis, including the handling of missing data, transformations, other data handling procedures, and analytical methodology will be provided in the Statistical Analysis Plan (SAP). Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses of safety data will be performed on all enrolled patients who receive at least 1 dose of study drug. Analyses of preliminary clinical activity will require at least one follow-up tumor assessment scan. <u>Safety Analyses</u> Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher and assessed for severity using NCI CTCAE version 5.0. Adverse events will be summarized by system organ class and preferred term and presented in

	decreasing order of incidence. Dose-limiting toxicities will also be summarized by dose and cohort. Vital signs, ECG data, ophthalmology, hematology, serum chemistry, coagulation, and urinalysis parameters from baseline and during study will be examined. Treatment-emergent changes in key laboratory parameters will be identified. Clinical laboratory data will be summarized for each time point that specimens are collected. Changes from baseline for select clinical laboratory analytes may also be explored as specified in the SAP. <u>Pharmacokinetic Analyses</u> Pharmacokinetic parameters will be calculated using a non-compartmental method from the PK samples collected during Cycles 1 and 2 and will include, but is not limited to C_{max}, AUC, $t_{1/2}$, Cl, T_{max}, and V_d. To describe the dependency on dose, scatter plots of C_{max} and AUC versus dose will be provided. Summary statistics will be tabulated for the trough concentration (C_{min}) and peak concentrations (end of infusion) by dose and study day. Pharmacometric methods may also be applied to further investigate OBI-999 and MMAE exposure (e.g., accumulation of OBI-999, presence of dose- or time-dependent OBI-999 PK behavior, verification of influential factors on OBI-999 PK). <u>Clinical Activity Analyses</u> Objective response rate (ORR) is defined as the percentage of patients with confirmed partial response (PR) or complete response (CR) according to RECIST 1.1. The CBR is defined as the percentage of patients with confirmed CR, PR, or stable disease. The DOR is defined as time from the date of reported confirmed PR or CR to the date of progression will be summarized descriptively using time-oriented summary statistics. Additionally, a listing of DOR for those patients experiencing response will be provided. The PFS is defined as the time from first dose of study drug until radiographically determined disease progression or death due to any cause, whichever event occurs first. Patients who are still alive or who have no progressive disease reported at analysis will be censored at their last evaluable tumor assessment. Kaplan-Meier estimates and 95% confidence intervals will be presented for time to event endpoints such as PFS if sufficient numbers of events to calculate meaningful statistics are observed.

2 Table of Contents

2.1 In-Text Tables

2.2 List of Figures

3 List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ADA	anti-drug antibody
ART	anti-retroviral therapy
AUC	area under the concentration curve
CBR	clinical benefit rate
CDX	cell line derived xenograft
Cl	clearance
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration
C_{min}	trough concentration
CNS	central nervous system
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
DCF	Data Clarification Form
DLT	dose-limiting toxicity
DOR	duration of response
DP	drug product
DS	drug substance
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
FACS	fluorescence-activated cell sorting
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
ADA	anti-drug antibody
HED	human equivalent dose
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IRB	Institutional Review Board
IV	intravenous(ly)
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
ORR	objective response rate
PDX	patient-derived xenograft
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Sprague Dawley
SPECT	single-photon emission computed tomography
SRC	Safety Review Committee
$t_{1/2}$	elimination half-life
TAb	total antibody

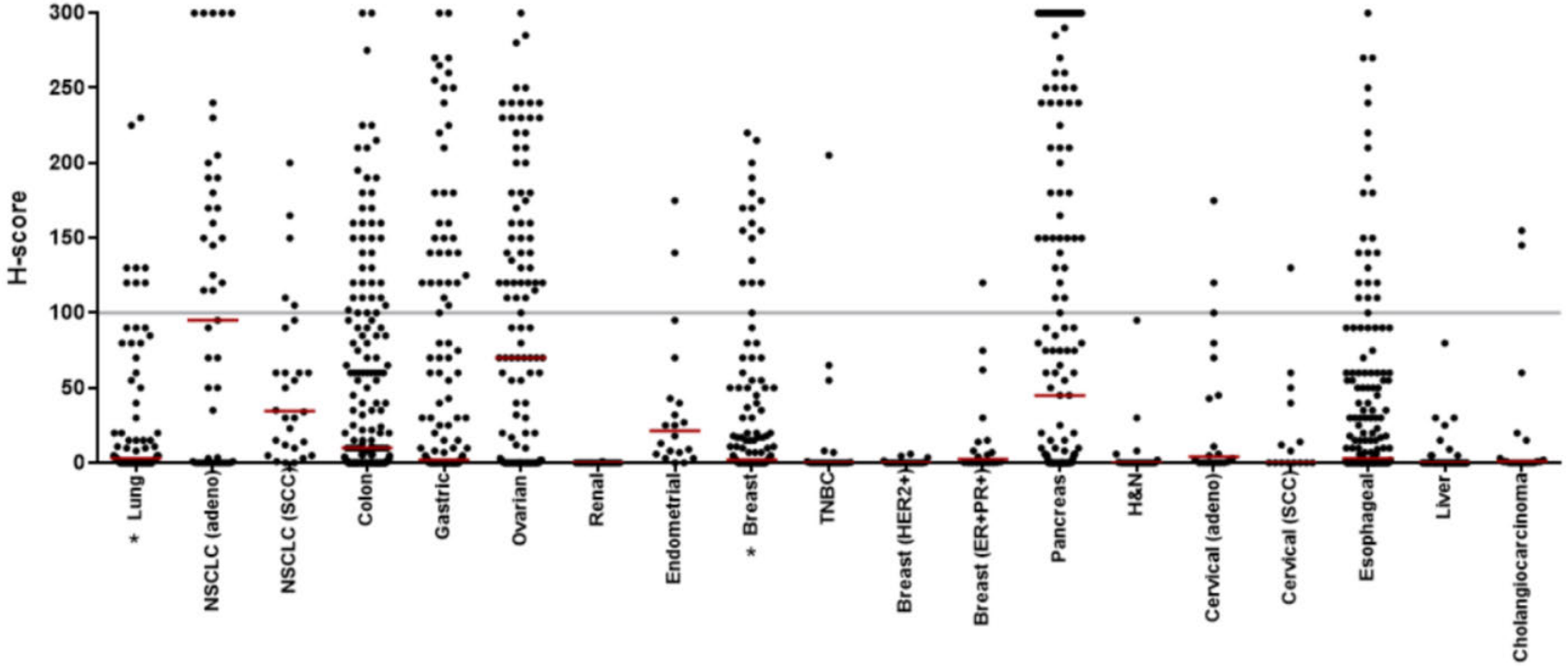
Abbreviation	**Definition**
ADA	anti-drug antibody
TACA	tumor-associated carbohydrate antigen
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
T_{max}	time to reach maximum concentration
ULN	upper limit of normal
V_d	volume of distribution
WHO	World Health Organization

4 Introduction

4.1 Globo H as Tumor-Associated Carbohydrate Antigen

Globo H is a neutral hexasaccharide (Fucα1→2Ga1β1→3GalNAcβ1→3Ga1α1→4Ga1β1→4G1cβ1) glycosphingolipid that was originally isolated from the human breast cancer cell line MCF-7 (Menard, et al., 1983; Bremer, et al. 1984). Its overexpression has been seen on a variety of epithelial cell tumors such as colon, ovarian, gastric, pancreatic, endometrial, lung, prostate, and breast cancers using monoclonal antibodies (mAbs), MBrl (immunoglobulin M [lgM]) (Menard, et al., 1983; Bremer, et al. 1984; Canevari, et al., 1983) and VK-9 (immunoglobulin G [IgG] 3) (Ragupathi, et al., 1999). Globo H is considered to be a tumor-associated carbohydrate antigen (TACA). Figure 4-1 shows the prevalence of Globo H expression in various cancer types from tumor specimens and tumor tissue microarray using a validated immunohistochemical (IHC) assay with an H-score cut-off of 100 (i.e., H-score ≥ 100) (Globo H IHC Pan-Tumor Validation Summary and Globo H IHC Pan Tumor Expanded Precision Validation Summary, as well as in-house preliminary data).

Figure 4-1 Globo H H-score in Various Tumor Tissues



Cancer Type	Lung*	NSCLC (adeno)	NSCLC (SCC)	Colon	Gastric	Ovarian	Renal	Endo-metrial	Breast*	TNBC	Breast (HER2+)	Breast (ER+PR+)	Pancreas	H&N	Cervical (adeno)	Cervical (SCC)	Esopha-geal	Liver	Cholan-giocarci-noma
Specimen	77	45	28	191	133	118	20	20	131	20	20	20	139	20	20	15	186	70	20
Median	3.0	95.0	34.5	10.0	2.0	70.0	0.0	21.5	2.0	0.1	0.1	2.5	45.0	0.1	4.0	0.0	3.0	0.0	1.0
Prevalence of cut-off ≥100	10.4%	48.9%	17.9%	20.9%	25.6%	33.1%	0.0%	10.0%	13.0%	5.0%	0.0%	5.0%	32.4%	0.0%	15.0%	6.7%	12.4%	0.0%	10.0%

Gray line: H-score cut-off; Red bar: median H-score

* Tumor samples without cancer subtype information

Note: Globo H H-score was determined using a validated immunohistochemistry assay.

In normal tissues, Globo H is weakly expressed in apical epithelial cells of lumen border, a site which is generally inaccessible to the immune system. Globo H ceramide sheds from tumor cells and may act as an immune checkpoint molecule to facilitate the escape of cancer cells from immune surveillance, thereby inhibiting the activation of immune cells (Tsai, et al., 2013). Incorporation of Globo H ceramide by endothelial cells results in enhanced angiogenic activity to promote tumor growth (Cheng, et al., 2014).

4.2 Background on OBI-999

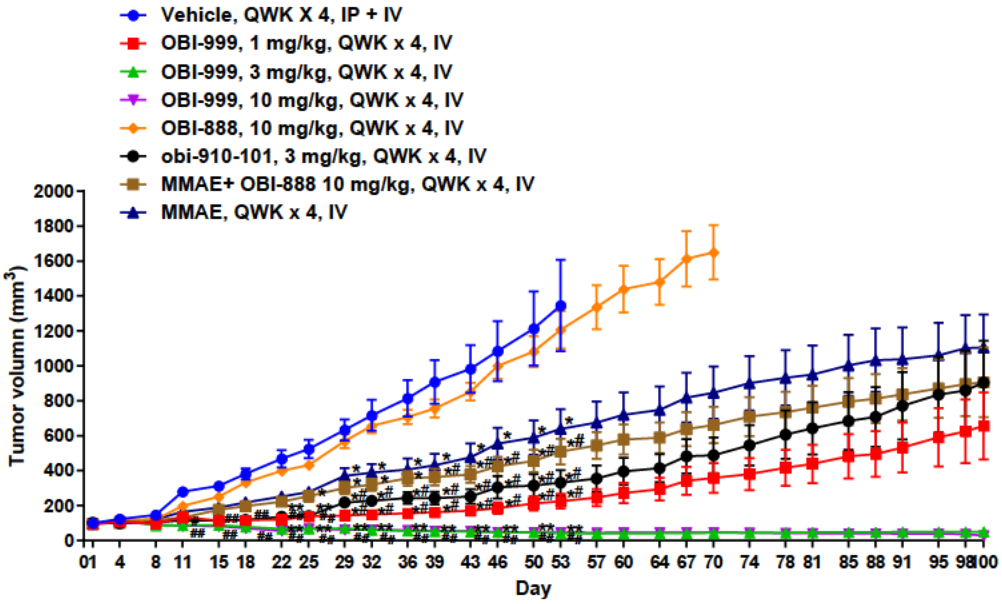
OBI-999, an antibody drug conjugate (ADC), is composed of a humanized monoclonal IgG1 antibody conjugated with monomethyl auristatin E (MMAE, vedotin), targeting Globo H for the treatment of Globo-H over-expressing cancers. The naked anti-Globo H antibody named OBI-888 is an investigational new drug (IND# 136961) currently in Phase 1 clinical trial. MMAE is an ultrapotent antimitotic agent that causes cell cycle arrest by inhibiting the polymerization of tubulin (Francisco et al., 2003; Doronina et al., 2003). The Thiobridge™ conjugate vcPAB linker connecting MMAE to the mAb is stable in extracellular fluid. The binding affinity and specificity of OBI-999 to Globo H have been demonstrated by enzyme-linked immunosorbent assay (ELISA) and fluorescence-activated cell sorting (FACS). Upon binding to Globo H, OBI-999 is internalized into the cell and delivered to lysosomes where the linker is cleaved by cathepsin, releasing the antimitotic MMAE. These evidences support that OBI-999 exhibits tumor-killing activity via internalization and lysosome dependent, protease mediated cytotoxicity of MMAE.

4.3 Nonclinical Studies

4.3.1 In Vivo Efficacy

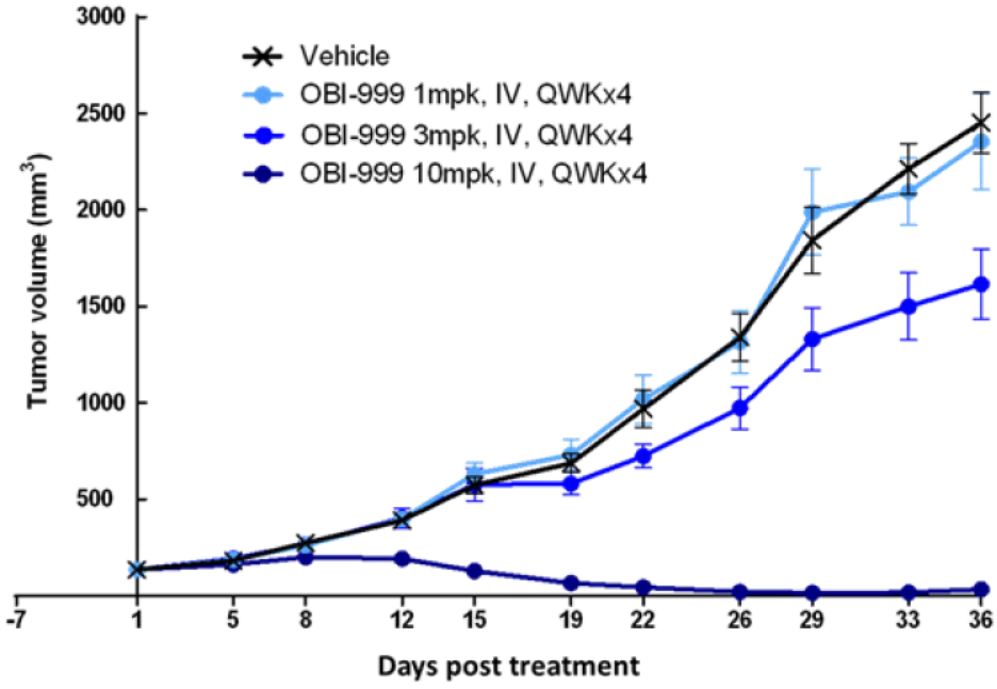
OBI-999 showed potent and long lasting anti-tumor efficacy, with tumor growth inhibition (TGI) ranging between 85–118% in multiple cell line derived xenograft (CDX) models, including MCF7 breast cancer, NCI-N87 gastric cancer, NCI-H526 small cell lung cancer, and HPAC pancreatic cancer, as well as the LU-01-0266 non-small cell lung cancer patient-derived xenograft (PDX) model. Globo H expression levels in the CDX and PDX models were approximately 57-99% and 27%, respectively. Most importantly, in the NCI-N87 gastric cancer CDX model, 1 day after implanting 2.5 x 10^6 cells, OBI-999 was administered at doses of 1, 3, or 10 mg/kg once weekly for 4 weeks; the percent TGI reached 83%, 97% and 97% on Day 53 (about 1 month after the last injection) (Figure 4-2). In the HPAC pancreatic cancer CDX model, on Day 7 after implanting 3 x 10^6 cells, OBI-999 was administered at a dose of 1, 3, and 10 mg/kg once weekly for 4 weeks; the maximum percent TGI was 104% on Day 36 post-treatment (Figure 4-3). OBI-999 was well tolerated and no significant changes in body weight were observed over the course of the study compared with the vehicle group. No overt toxicities were observed during the study period. Additional details are provided in the [OBI-999 Investigators' Brochure].

Figure 4-2 Effect of OBI-999, OBI-888, OBI-910-101 and MMAE on Tumor Growth in Nude Mice Inoculated with NCI-N87 Human Gastric Cancer Cells



Note: OBI-910-101 is anti-CD30 conjugated with MMAE serving as a control ADC

Figure 4-3 Effect of OBI-999 on Tumor Growth in Nude Mice Inoculated with HPAC Human Pancreatic Cancer Cells



Note: The anti-tumor efficacy was evaluated at doses of 1, 3, or 10 mg/kg of OBI-999 via intravenously injection once weekly for four weeks. The study utilized 8 mice per group.

4.3.2 Tumor Targeting

OBI-999's tumor targeting ability has been demonstrated by biodistribution and single-photon emission computed tomography (SPECT) imaging in NCI-N87 xenograft mice. At 168 hours post-injection, the tumor/muscle ratio reached 16.25, indicating that OBI-999 targeted and accumulated in Globo H expressing tumors. At one-hour post-injection, OBI-999 accumulated mostly in blood-rich organs, including lung, liver, spleen, and kidney. The concentration of OBI-999 in these organs gradually decreased with blood clearance. The biodistribution pattern in organs was similar between normal mice and tumor-bearing mice. Although a certain amount of 111In-DTPA-labeled OBI-999 were observed in the female genital system, no specific binding was found in tissue-cross-reactivity of the parental antibody, OBI-888, in humans.

Good laboratory practice (GLP) tissue-cross-reactivity studies of OBI-888 were conducted on human and monkey tissues to determine the potential cross-reactivity of OBI-888 with human cryosections and cynomolgus monkey tissues. OBI-888-specific staining was most frequently observed in the luminal epithelium, which is consistent with the Globo H expression pattern in tissues. The above studies support the tumor targeting ability of OBI-999.

4.3.3 Pharmacokinetics

The pharmacokinetics (PK) of OBI-999 were evaluated in normal and tumor bearing mice, rats and monkeys following intravenous (IV) administration of OBI-999. Serum samples were analyzed for total antibody (TAb), intact ADC (OBI-999) and free MMAE. In these species, exposure of OBI-999 increased with dose proportionally. No sex difference was observed across the dose ranges. No accumulation was observed following the repeated dosing of OBI-999. Total antibody exposure was similar to those of OBI-999. Limited systemic exposure of free MMAE was observed, indicating that OBI-999 was stable in serum after administration to animals. In vitro serum stability revealed that free MMAE levels produced from OBI-999 in human serum was very limited, and the payload-antibody conjugation of OBI-999 is shown to be stable in human serum.

4.3.4 Safety Pharmacology

Evaluation of the cardiovascular system (blood pressure and electrocardiogram), respiratory function (respiration rates and pulse oximetry) and central nervous system (CNS) effects (neurological examination) were incorporated into the 3-week repeated dose study in cynomolgus monkeys. No adverse events were observed at doses up to 10 mg/kg. OBI-999 was well-tolerated in monkeys with no undesired pharmacological effects on cardiovascular, respiratory, and CNS functions.

4.3.5 Toxicology

Single-dose and multiple-dose GLP toxicology studies were carried out in Sprague Dawley (SD) rats and Cynomolgus monkeys. Both species are considered relevant species due to a Globo H expression pattern similar to humans.

Sprague Dawley rats were administered single doses of 0, 3, 10, or 30 mg/kg OBI-999 by slow IV injection (5 to 10 minutes/animal) at a volume of 10 mL/kg. Animals were observed for 14 treatment-free days and sacrificed on Day 15. A single dose of OBI-999 caused effects on hematopoietic and male reproductive system in SD rats. Hematologic changes included decreased red blood cell parameters responded by increased reticulocyte counts and splenic

extramedullary hematopoiesis at 30 mg/kg in both sexes, suggesting potential toxicity on bone marrow. Male rats administered 10 or 30 mg/kg showed decreased testis size and weights that correlate with microscopic degenerative findings. Exposure of OBI-999 increased with dose proportionally. No gender difference was observed across the dose range. Total antibody exposure was generally greater than exposures to conjugated antibody. Systemic exposure to free MMAE was limited. The no observed adverse effect level (NOAEL) was considered to be 3 mg/kg.

Sprague Dawley rats were administered 0, 3, 10, or 30 mg/kg OBI-999 (N = 10/sex/group for main study) once every 3 weeks for 3 weeks (2 total doses) by slow bolus infusion followed by a 3-week recovery period. OBI-999-related reversible effects on body weight, body weight gain, food consumption, and ophthalmology were observed in animals administered 30 mg/kg. Hematologic effects were identified in males administered 30 mg/kg and females administered ≥10 mg/kg and generally reversed after 3 weeks of recovery. These effects were likely associated with bone marrow suppression at the terminal sacrifice and a physiologic hematopoietic response at the recovery sacrifice. OBI-999-related effects on male reproductive system including degeneration/atrophy of the seminiferous tubules, testis, and prostate, and hypospermia in the epididymis were observed at level ≥10 mg/kg/dose. OBI-999-related effects on clinical chemistry results were identified in animals administered 30 mg/kg/dose. These effects including higher cholesterol and triglycerides, lower albumin, and higher aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were small in magnitude and generally reversible. The NOAEL in SD rats was 3 mg/kg/dose.

Cynomolgus monkeys were administered single doses of 0, 10, or 30 mg/kg OBI-999 (N = 1/sex/group) by slow bolus IV injection at a volume of 6 mL/kg. Animals were observed for 14 treatment-free days to assess the reversibility, persistence, or delayed occurrence of effects. OBI-999-related mortality was observed in the male and female monkey on Day 6 at the level of 30 mg/kg. All other animals survived to scheduled sacrifice. Hematologic effects in animals administered 10 mg/kg were maximal on Day 10 with improvement on Day 15, suggesting reversibility. The highest non-severely toxic dose (HNSTD) was 10 mg/kg due to the marked severity of hematologic findings and the lack of evidence of lethality or life-threatening toxicities in animals administered 10 mg/kg.

Cynomolgus monkeys were administered vehicle control article (OBI Formulation Buffer) or 2, 5, or 10 mg/kg/dose OBI-999 (N = 3/sex/group for main study) once every 3 weeks via IV infusion followed by a 3-week recovery period. OBI-999-related decreases in body weight and food consumption were observed for animals administered 10 mg/kg/dose. These findings showed evidence of reversibility during the recovery period. OBI-999-related bone marrow suppression was dose-dependent and reversible during the recovery period. OBI-999 related non-adverse microscopic findings included decreased lymphocytes and/or increased lymphocyte apoptosis of the thymus in animals administered ≥2 mg/kg/dose; decreased myeloid cellularity of the bone marrow in animals administered ≥5 mg/kg/dose. Thus, the HNSTD was 10 mg/kg/dose. This dose level corresponded to mean peak concentration (C_{max}) and area under the concentration time curve (AUC) values of 210 µg/mL and 9730 µg x hr/mL, respectively, in males and 217 µg/mL and 9680 µg x hr/mL, respectively, in females on Day 1 of the dosing phase.

Additional details are provided in the [OBI-999 Investigators' Brochure].

4.4 Clinical Risks/Benefits of OBI-999

OBI-999 is an ADC composed of a humanized monoclonal IgG1 antibody conjugated with MMAE. Toxicities may include myelosuppression and neuropathy as these side effects have been observed with other ADCs based on the MMAE molecule. A complete discussion of guidance for the investigator is provided in the OBI-999 Investigator Brochure.

The risk-to-benefit ratio for this study is considered acceptable based upon the patient population, the available limited treatment options for patients with advanced solid tumors, the toxicology results and activity data observed in the preclinical safety studies, and the results of the Dose Escalation Phase of this study.

As of 02 June 2020, 13 out of 15 patients enrolled in Part A had an investigator driven tumor response assessment. The best overall response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria was stable disease, which was observed in 5 patients, including 1 patient from Cohort 1 (0.4 mg/kg with rectal cancer), 2 patients from Cohort 2 (0.8 mg/kg; 1 with pancreatic cancer and 1 with esophageal cancer), and 2 patients from Cohort 3 (1.2 mg/kg; 1 with head and neck cancer and 1 with cancer of the appendix). However, due to the limited sample size in Part A (Dose-Escalation), a relationship between Globo H expression level and depth of clinical activity at the Recommended Phase 2 Dose (RP2D) has yet to be established in this patient population. This relationship will be further evaluated in Part B of the study at the RP2D of 1.2 mg/kg.

4.5 Rationale

Globo H is a hexasaccharide glycosphingolipid located endogenously on the outer membrane of epithelial cells and was first identified in breast cancer cells. Globo H was found to be overexpressed on the cell surface of several epithelial cancers such as breast, pancreatic, ovarian, endometrial, gastric, lung, and prostate cancers. Globo H has been associated with tumor stem cells, as a potent inducer of angiogenesis and immune suppressor through Notch signaling, rendering it a target for cancer therapy (Cheng, et al., 2014).

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

4.5.1 Rationale for Selection of Study Population

The target population enrolled in Part A includes patients with advanced solid tumors refractory to at least one line of systemic therapy or intolerable with standard therapy or for which no standard treatment is available, regardless of Globo H status. The RP2D has been established based on dose limiting toxicities (DLTs), with consideration of the overall toxicities and available PK data from the dose-escalation phase of the study.

Part B is being initiated to obtain additional safety data, and assess the preliminary clinical activity profile of OBI-999 in patients with advanced solid tumors that have evidence of Globo H overexpression using a validated immunohistochemistry assay, and hence a potentially enhanced likelihood of seeing objective responses. In addition to any cancer type with a Globo H H-score ≥ 100, gastrointestinal tumor types with reasonable frequencies of Globo H overexpression, based on available tissue microarray samples, were selected for evaluation, including pancreatic and colorectal cancer.

4.5.2 Rationale for Dose Selection

4.5.2.1 Selection of Doses for Dose Escalation (Part A)

The dose levels for Part A resulted from calculations based on data from preclinical studies and knowledge of the DLTs and recommended doses for other MMAE-based ADCs. The first-in-human starting dose was determined by using 1/6th the human equivalent dose (HED) of the HNSTD observed in non-human primates. The HNSTD in cynomolgus monkeys was 10 mg/kg, equivalent to a HED of 3.24 mg/kg. One sixth of this is equal to 0.54 mg/kg. To be conservative, an additional safety margin was applied and the initial dose chosen for this study was 0.4 mg/kg administered on Day 1 of every 21-day cycle.

Based on FDA feedback (Pre-Investigational New Drug Application #143960 Meeting Request Written Responses, dated 12 June 2019), the dose levels of OBI-999 that were to be evaluated in Part A (0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg [capping calculations at a maximum of 100 kg]) were similar to the dose ranges used by other MMAE-bearing ADCs.

4.5.2.2 Selection of the Recommended Phase 2 Dose

As of 02 June 2021, the Dose-Escalation Phase of this study was completed after enrolling a total of 15 patients with diverse solid tumors, including 3 patients each for Cohorts 1, 2, and 4 (0.4, 0.8 and 1.6 mg/kg), and 6 patients for Cohort 3 (1.2 mg/kg). Patients were treated with OBI-999 on Day 1 of a 21-day cycle.

All 3 patients in Cohort 4 (1.6 mg/kg) developed Grade 4 neutropenia, with details as follows:

- Patient U01-016 had Grade 4 neutropenia (preferred term neutropenia) that was serious and met DLT criteria (lasting greater than 7 days).
- Patient U01-018 had Grade 4 neutropenia (preferred term neutropenia) which was serious, required hospitalization, and was accompanied by Grade 4 acute kidney injury, Grade 4 respiratory distress, Grade 4 hypocalcemia, and Grade 4 multi-organ failure. All of these events were considered related to study therapy. The patient was discontinued due to clinical progression of the disease.
- Patient U01-017 had Grade 4 neutropenia (preferred term neutropenia) which was serious and required hospitalization.

All 3 events of Grade 4 neutropenia were considered likely related to OBI-999, with 1 event meeting the DLT criteria (Patient U01-016). Based on these findings, the 1.6 mg/kg dose level was considered to have exceeded the MTD.

Based on the design of the Dose-Escalation Phase, 3 additional patients (total of 6 patients) were enrolled at the next lower dose level (Cohort 3; 1.2 mg/kg) to confirm the MTD and establish the RP2D. In Cohort 3 (1.2 mg/kg), no events of Grade 4 neutropenia were observed, none of the 6 patients had a DLT, and administration of 1.2 mg/kg OBI-999 was generally well tolerated.

Pharmacokinetic results revealed that OBI-999 exhibited nonlinear clearance at doses lower than 1.2 mg/kg. The exposure of the active metabolite, MMAE, was extremely high at a dose of 1.6 mg/kg and generally comparable at doses less than or equal to 1.2 mg/kg (Table 4-1).

Based on these findings, 1.2 mg/kg administered on Day 1 of a 21-day cycle was selected as the RP2D. This dose allows for effective dose reduction in Part B (Expansion Cohort) in the event that unacceptable toxicities are observed at the RP2D.

Table 4-1 Pharmacokinetic Summary – Part A of OBI-999-001

		MMAE				OBI-999				
Cohort	Dose (mg/kg)	T_{max} (d)	C_{max} (ng/mL)	AUC (ng*d/mL)	$T_{1/2}$ (d)	C_{max} (µg/mL)	AUC (µg*d/mL)	Cl (L/day)	$T_{1/2}$ (d)	Vd (L)
1	0.4	0.79	2.7	12.5	2.66	5.9	6	5.3	1.8	8.2
2	0.8	0.38	3.9	16.5	3.51	11.3	15.8	4.2	3.9	8
3	1.2*	0.59	3.9	16.6	2.96	20.6	29.9	2.8	3.6	6.8
4	1.6	2.79	7.6	53.6	3.09	33.7	60.4	2.6	2	5.7

*data calculated from 5 subjects dosing at 1.2 mg/kg.

5 Study Objectives and Endpoints

5.1 Study Objectives

5.1.1 Primary Objectives

The primary objectives are:

- To determine the safety and tolerability of OBI-999 when administered IV to patients with advanced solid tumors.
- To determine the MTD and RP2D of OBI-999.

5.1.2 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 PK of OBI-999 and its active metabolite MMAE.

5.1.3 Exploratory Objectives

The exploratory objective is:

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

5.2 Study Endpoints

5.2.1 Part A – Dose Escalation

5.2.1.1 Primary Endpoints

- Adverse events (AEs)/serious adverse events (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.

5.2.1.2 Secondary Endpoint

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

5.2.1.3 Exploratory Endpoint

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

5.2.2 Part B – Expansion Cohort

5.2.2.1 Primary Endpoints

- Percentage of patients with objective response, clinical benefit, DOR and PFS according to RECIST 1.1.
- Percentage of patients with ADAs in blood.

5.2.2.2 Secondary Endpoints

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

5.2.2.3 Exploratory Endpoints

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

6 Investigational Plan

6.1 Description of Overall Study Design and Plan

This is a Phase 1/2, open-label, dose-escalation, and cohort-expansion study of OBI-999, an 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.

Safety Review Committee (SRC) meetings were conducted throughout Part A of the study. The SRC reviewed the safety data (AEs and laboratory toxicities) of each lower level dose cohort before proceeding to the next dose level during Part A. At the end of Part A, the SRC reviewed the safety and PK data to confirm the MTD and establish the RP2D before start of Part B, as specified in a separate charter.

During Part B, the SRC will continue to monitor the severity and frequency of acute and cumulative toxicities at regular intervals, e.g., every 3 months, to ensure acceptable tolerability of the selected RP2D and of the effectiveness of dose modification rules.

6.1.1 Part A – Dose-Escalation

Up to 30 eligible patients with advanced solid tumors will be enrolled in Part A. No Globo H expression testing will be 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 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 AE will be 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.

6.1.1.1 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 Section 6.2), or
- Related SAEs (Refer to Section 8.2.3 & Section 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.

6.1.2 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 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 type 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.

6.1.3 Duration of Study

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.

6.2 Definition of Dose-Limiting Toxicities (Part A only)

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 that does not resolve to Grade 1 or Baseline within 72 hours despite optimal supportive care.
- Any Grade 4 gastrointestinal (GI) toxicity.
- 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).

All AEs unless they are determined to be not related to study drug will be taken into consideration in determining DLTs. NCI CTCAE version 5.0 will be the basis for the descriptive terminology and grading of AEs. The period for DLT observation is 21 days from the start of first dose of OBI-999 (i.e., Day 1).

6.3 Discussion of Study Design

This study will be undertaken in patients with advanced cancer that has progressed on prior therapy. In this setting, patients will be seeking to alleviate symptoms of their fatal disease and prolong life through exposure to a novel agent.

Patient safety, and a favorable risk/benefit balance, will be carefully monitored throughout and after treatment. Additionally, attention will be taken to enroll only patients who are felt to be in sufficient condition to undertake this clinical trial, as defined by adequate performance status, suitable baseline organ function, and the Investigator's determination that there are no significant comorbid conditions which present undue risk. Nevertheless, unexpected toxicity of the investigational drug may occur, and all patients will have informed consent prior to treatment.

7 Selection and Withdrawal of Patients

7.1 Inclusion and Exclusion Criteria

7.1.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the study (for both Parts A and B unless specified otherwise):

1. Male or female patients, 18 years of age or older at the time of consent.
2. Provide written informed consent prior to performing any study-related procedure.
3. Histologically or cytologically confirmed patients with advanced solid tumors.

4. Patients must have been treated with established standard-of-care therapy, or physicians have determined that such established therapy is not sufficiently efficacious, or patients have declined to receive standard-of-care therapy. In the latter case, the informed consent must state the effective therapies the patient is declining.
5. Measurable disease (i.e., at least one measurable lesion per RECIST 1.1) (Eisenhauer, et al., 2009).
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Oken, et al., 1982).
7. Adequate organ function defined as:
   a. Hepatic:
      i. Serum ALT ≤3 × upper limit of normal (ULN), ≤5 × ULN in the presence of liver metastases
      ii. Serum AST ≤3 × ULN, ≤5 × ULN in presence of liver metastases
      iii. Serum bilirubin ≤1.5 × ULN (unless due to Gilbert's syndrome or hemolysis)
   b. Renal:
      i. Creatinine clearance >50 mL/minute using Cockcroft Gault equation
   c. Hematologic:
      i. Absolute neutrophil count ≥1,500/µL
      ii. Platelets ≥100,000/µL
      iii. Hemoglobin ≥8 g/dL
8. Patient is willing and able to comply with all protocol-required assessments, visits, and procedures, including a pretreatment tumor biopsy. Archival tumor biopsies are acceptable at baseline.
9. Females of childbearing potential must have negative serum pregnancy test prior to starting study therapy, and agree to use a reliable form of contraceptive during the study treatment period and for at least 120 days following the last dose of study drug.

   Patient not of childbearing potential (i.e., permanently sterilized, postmenopausal) can be included in study. Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

   Male patients must agree to use an adequate method of contraception during the study treatment period and for at least 120 days following the last dose of study drug.
10. Cannot be breast feeding.
11. Patients with human immunodeficiency virus (HIV) infection are eligible if CD4+ T-cell counts ≥ 350 cells/µL; patients on antiretroviral therapy (ART) should be on an established dose for at least 4 weeks and have an HIV viral load less than 400 copies/mL prior to enrollment.
12. Patients with serological evidence of chronic hepatitis B virus (HBV) infection are eligible if they have an HBV viral load below the limit of quantification with or without concurrent viral suppressive therapy.
13. Patients with a history of hepatitis C virus (HCV) infection should have completed curative antiviral treatment and have a viral load below the limit of quantification.

14. Patients in Part B (Cohort-Expansion) must have documented Globo H H-score ≥ 100 from a qualified laboratory IHC assay in one of the following tumor types to be enrolled in the respective cohort:
    - Cohort 1: Pancreatic cancer
        - Histopathologically confirmed patients with metastatic adenocarcinoma of the pancreas.
    - Cohort 2: Colorectal cancer
        - Histopathologically confirmed patients with metastatic colorectal adenocarcinoma.
    - Cohort 3: Basket (any solid tumor type other than those included in Cohorts 1 and 2)
        - Histologically or cytologically confirmed patients with advanced solid tumors.

7.1.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible to participate in this study:

1. Less than 3 weeks from prior cytotoxic chemotherapy or radiation therapy; and less than 5 half-lives or 3 weeks, whichever is shorter, from prior biologic therapies, prior to the first dose of OBI-999.
2. Has undergone a major surgical procedure (as defined by the Investigator) or significant traumatic injury within 28 days prior to the first dose of OBI-999.
3. Sensory or motor neuropathy of Grade 2 or greater.
4. Patients with a history of solid organ transplant.
5. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Grade 0 or 1 (using NCI CTCAE version 5.0), except for alopecia and laboratory values listed in the inclusion criteria.
6. Receipt of any prior therapy targeting Globo H.
7. Known hypersensitivity to OBI-999 or its excipients.
8. Has known untreated central nervous system metastases. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period.
9. Has significant clinical cardiac abnormality (e.g., clinical heart failure or unstable angina).
10. Any medical co-morbidity that is life-threatening or, in the opinion of the Investigator, renders the patient unsuitable for participation in a clinical trial due to possible noncompliance, would place the patient at an unacceptable risk and/or potential to affect interpretation of results of the study.
11. Is receiving any concurrent prohibited medication as listed in Section 8.6.3.

7.2 Treatment Discontinuation and Withdrawal of Patients

A patient who withdraws from the study within the DLT evaluation period for reasons other than drug related AE will be replaced.

A patient may voluntarily withdraw or be withdrawn from the study treatment at any time for reasons including, but not limited to, the following:

- Progressive disease.
- Grade 4 infusion reactions and OBI-999-related toxicity.
- Dose reductions required on more than 2 occasions for toxicity related to OBI-999.
- Treatment interruption for more than 2 consecutive doses for related or unrelated reasons.
- Patient withdrawal of consent: At any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment.
- Inter-current illness: A condition, injury, or disease unrelated to the primary diagnosis that becomes apparent during treatment and necessitated the patient's termination from the study.
- General or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria.
- Protocol deviation: The patient's findings or conduct fail to meet the protocol entry criteria or fail to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits) such that the Sponsor and the Investigator agree that the deviation necessitates premature termination from the study.
- Lost to follow-up: The patient stops coming for visits, and study personnel are unable to contact the patient.

7.3 Follow-Up for Drug Discontinuation/Patient Withdrawal from Study

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the Sponsor. The date and the reason for study treatment discontinuation / study withdrawal must be recorded on the electronic case report form (eCRF). Patients who withdraw prematurely are to attend an early termination visit, if possible, and complete all assessments.

In the event that a patient discontinues prematurely from the study due to a treatment-emergent adverse event (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a patient is withdrawn from the study, the patient may not re-enter the study.

8 Treatments

8.1 Details of Study Treatment

OBI-999 is an ADC composed of a Globo H-targeting humanized IgG1 mAb (OBI-888; IND #136,961), which is covalently linked to MMAE by a cathepsin B protease cleavable linker. Globo H is a TACA.

OBI-999 drug product (DP) liquid is packaged in a single-use 10 mL transparent borosilicate type 1 glass vial for IV infusion. Each vial of OBI-999 DP liquid contains 5 mL of 5 mg/mL OBI-999 drug substance (DS) in a pH 6.0 solution formulated with 25 mM sodium citrate, 150 mM Arginine, and 0.02 % (w/v) Polysorbate 80. OBI-999 DP is diluted to the appropriate concentration in 0.9 % sodium chloride or 5% glucose prior to administration by IV infusion.

All study drug will be supplied by OBI Pharma Inc., and must remain under adequate security and proper storage conditions. Do not use study drug after the expiration date, which is imprinted on the drug container.

The OBI-999 DP should be administered to the study subjects within 4 hours of reconstitution at room temperature. Overall storage of the DP material should not exceed 8 hours at room temperature. Refer to Appendix 1 for details of dispensing, volume needed, mixing and reconstitution of OBI-999.

8.1.1 Packaging and Labeling

OBI-999 drug product will be packaged in carton boxes. Each box will contain ten OBI-999 vials. The labels on each kit will meet the applicable regulatory requirements for each country.

OBI-999 will be packaged and labeled according to current Good Manufacturing Practices (GMP) guidelines. Details of the packaging and labeling are provided in the Pharmacy Manual.

8.1.2 Storage

OBI-999 drug product must be stored at a temperature of 2 to 8°C.

8.2 Treatment Regimen

8.2.1 OBI-999 Doses

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).

8.2.2 OBI-999 Administration

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.

8.2.3 Prophylactic Measures

Approximately 30 to 60 minutes prior to OBI-999 administration, all patients should receive prophylactic treatment for infusion reactions. Prophylactic treatments include acetaminophen orally and diphenhydramine (or equivalent) orally or IV (recommended doses are: acetaminophen 650 mg, diphenhydramine 50 mg). If an alternative premedication regimen is thought to be required, Sponsor approval should be sought.

For patients who experience an infusion reaction despite initial premedication, additional prophylactic treatment may be added prior to subsequent doses, including an H2 blocker such as ranitidine, and/or corticosteroids.

Prophylactic treatment for infusion reactions may be withheld at the Investigator's discretion if no infusion reactions were observed with the first cycle of treatment. Additional details are provided in Section 8.3.1.1.

8.3 Dose Modifications and Toxicity Management

Escalation to a higher OBI-999 dose cohort is not permitted during the study.

Dose modifications for hematologic toxicity, non-hematologic toxicity, and infusion reactions should be independently assessed at each visit. Recommendations for dose modifications for toxicity are provided in Table 8-1.

Table 8-1 OBI-999 Dose Modifications for Toxicity

Toxicity	Hold Dose	% of Full Dose after Recovery to Grade 0-1
Grade 1	Do not hold dose	100
Grade 2	Hold dose until resolution to Grade 0 or 1	75
Grade 3	Hold dose until resolution to Grade 0 or 1	75
Grade 4	Treatment should be discontinued	Not applicable

Once the dose has been reduced for toxicity and found to be well tolerated, re-escalation may be permitted at the Investigator's discretion. If a patient requires dose reductions on more than 2 occasions for toxicity related to OBI-999, the patient should discontinue from the study.

All reasons for treatment modifications should be fully explained.

The study drug dose which is not administered within the permitted window period of ±3 days, must be skipped, and the next dose will be administered as per protocol schedule. Any skipped dose due to safety reason and if medically justified, for OBI-999 treatment related or unrelated reasons, will not be captured as a protocol deviation for this study.

Treatment interruption for more than 2 consecutive doses for related or unrelated reasons may necessitate discontinuation of study treatment.

Treatment interruption for intercurrent non-treatment related AEs will be at the Investigator's discretion and based on the well-being of the patient. All reasons for treatment interruption and

delays should be fully explained. Treatment for hematologic and non-hematologic toxicity may be implemented as clinically indicated according to institutional guidelines. Refer Table 8-2 for therapeutic antiemetic and anti-diarrheal recommendations.

Table 8-2 Therapeutic Antiemetic and Anti-Diarrheal Recommendations

Diarrhea and Abdominal Cramping	Nausea, Vomiting, or Anorexia
Dicyclomine: Recommended when the predominant issue is cramping or abdominal pain	1st line: 5HT3-inhibitors
Diphenoxylate/Atropine or/and Loperamide	2nd-line: Dexamethasone, ideally in combination with a 5HT3-inhibitor. Short term use can be very effective
	Other agents: anti-histamines; benzodiazepines; proton pump inhibitors; dopamine antagonists; cannabinoids
Hyoscine: Anti spasmodic agents helpful for abdominal cramping	
Budesonide (Entocort EC): Corticosteroid with limited systemic absorption; 9 mg once daily for up to 8-12 weeks	

8.3.1 Infusion Reactions

Signs/symptoms of infusion reactions may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritic/itching; rash/ desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

In the event of an infusion reaction, additional serum/plasma samples may be drawn at the time of the event to evaluate drug concentration and ADA, as well as to assess levels of cytokines and/or other markers of inflammation.

8.3.1.1 Management of Infusion Reactions

As stated in Section 8.2.3 all patients will receive prophylaxis prior to the first dose of treatment. If no infusion reactions occur with prophylactic treatments, these may be withheld for subsequent doses at the Investigator's discretion. Prophylactic treatment as described in Section 8.2.3 should be resumed for all future doses if subsequent dosing without prophylaxis is associated with infusion reactions.

In the event of an infusion reaction, the OBI-999 infusion should be interrupted and medical therapy administered according to institutional standard of care.

Patients who experience a Grade 1 or Grade 2 infusion reaction may resume the infusion of drug at a reduced infusion rate (30% to 50% slower than initial rate) on the same day following appropriate medical management, as long as this falls within the 4-hour drug administration window (see Section 8.1 and Appendix 1). If the 4-hour window from product reconstitution is exceeded, new drug may be prepared to administer the remainder of the planned dose.

Patients who experience a Grade 3 infusion reaction may be retreated at the discretion of the Investigator at the next scheduled treatment. Such patients should receive additional premedication that may include an acetaminophen, an antihistamine, or a corticosteroid.

Patients should be followed for at least 4 hours and until resolution of the infusion reaction. In person or telephonic follow up the next day should also be arranged to ensure there are no recurrent symptoms. Patients should also be instructed to contact study personnel if symptoms recur at later time points.

OBI-999 should be permanently discontinued in patients who experience a life-threatening (Grade 4) infusion reaction.

8.3.2 Peripheral Neuropathy

Signs/symptoms of peripheral neuropathy may include: hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness.

If peripheral neuropathy is observed, additional serum/plasma samples may be drawn at the time of the event to evaluate drug concentration and ADA, as well as to assess levels of cytokines and/or other markers of inflammation.

Peripheral neuropathy is a known adverse event from MMAE-based ADCs and can be expected to occur with OBI-999. Therefore, specific assessment for signs and symptoms of peripheral neuropathy should be performed at each physical exam. Patients who develop peripheral neuropathy should be followed until resolution in order to define the time to resolution of the neuropathy.

Additionally, non-symptomatic patients will continue to be monitored for possible signs and symptoms of peripheral neuropathy as part of the Safety Follow-Up period.

8.3.2.1 Management of Peripheral Neuropathy

For new or worsening Grade 2 or 3 peripheral neuropathy, OBI-999 dosing should be held until neuropathy improves to Grade 1 or baseline. OBI-999 dosing may be restarted at a reduced dose (75% of the full dose; see Table 8-1).

For Grade 4 peripheral neuropathy, OBI-999 should be permanently discontinued.

8.4 Study Treatment Assignment

During Part A, patients were assigned to a dose level in the order of study entry.

During Part B, all patients will receive a dose level of 1.2 mg/kg (capping administered dose to a maximum of 120 mg for 100 kg) of OBI-999.

8.5 Treatment Accountability and Compliance

All drug supplies will be provided by the Sponsor. Administration of study drug will be supervised by study personnel to ensure compliance.

8.6 Prior and Concomitant Illnesses and Medications

8.6.1 Prior and Concomitant Illnesses

Investigators should document all prior significant illnesses that the patient has experienced prior to screening. Additional illnesses present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

8.6.2 Prior and Concomitant Medications

All medications and other treatments taken by the patient prior to the start of the study at screening and treatments initiated during the study, must be recorded on the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

After the baseline visit, medication to treat minor illness(es) are generally permitted, including:

- Use of localized palliative radiation for pre-existing lesions to control pain, at the discretion of the physician.
- Corticosteroids use: topical, inhaled, ophthalmologic, intra-articular, or intranasal corticosteroids; systemic steroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent. For management of side effects including nausea or infusion reactions, intermittent prophylactic or therapeutic use of glucocorticoids is allowed at doses required for medical therapy administered according to institutional standard of care and at the Investigator's discretion.

8.6.3 Prohibited Medications

If there is a clinical indication for the use of one of the following prohibited medications, then discontinuation from the study drug may be required.

- Anti-neoplastic therapy, whether approved or experimental, including but are not limited to: chemotherapy, immunotherapy, surgery, radiotherapy are not allowed with OBI-999. **NOTE:** Use of localized palliative radiation for pre-existing lesions to control pain may be allowed at the discretion of the physician.
- Immunosuppressive therapy (e.g., cyclosporine, rapamycin, tacrolimus, cyclophosphamide, methotrexate, etc.).
- Systemic steroids of >10 mg/day prednisone or equivalent
- Any other concurrent investigational therapy, regardless of indication.
- Strong inhibitors or inducers of CYP3A (see Appendix 2)
- Clinical inhibitors of P-glycoprotein (see Appendix 3)

9 Study Procedures

Table 9-1 outlines the timing of procedures, and assessments to be performed throughout the study.

Table 9-2 and Table 9-3 outline the PK and ADA Sampling Schedules in Part A and Part B, respectively.

9.1 Patient Informed Consent

Prior to performing any study-related procedures, the Investigator (or his/her designated staff member) will obtain written informed consent from the patient. A separate biospecimen consent (pre-screening) for Globo H testing may be utilized in order to ensure that eligibility criterion is met for Part B patients prior to consenting the subject for the remaining eligibility-related procedures. This two-step consent process may streamline the screening process, ensuring timely availability of the Globo H result and avoiding having the patient consent for the remaining procedures until he/she is confirmed to have the requisite Globo H expression for study entry.

9.2 Procedures by Study Period

Assessments and study procedures are to be performed as outlined in the Schedule of Assessments, Table 9-1. The PK and ADA Sampling Schedules are provided in Table 9-2 (Part A) and Table 9-3 (Part B).

The Investigator may at his/her discretion arrange for a patient to have an unscheduled assessment, especially in the case of AEs that require follow-up or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page on the eCRF must be completed. Additional visits to follow-up positive ADA may happen after end of study (Table 9-1).

Table 9-1 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[j]	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 sample[n]			See footnote 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:
   - 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.
   - 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: 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: 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 9-2 (Part A) and Table 9-3 (Part B).

o. Immunogenicity studies (ADA) - ADA samples will be collected. Detailed sampling schedule in Table 9-2 (Part A) and Table 9-3 (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 9-2 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 9-3 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.

10 Clinical Activity Profile Assessments

Radiology (CT or MRI scan) evaluations (±7 days) of tumor response are to be performed during screening within 28 days prior to Cycle 1 Day 1 (first dose of study medication), and thereafter 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. Radiology assessment for end of study follow-up and early termination should be performed unless the patient already has radiographic confirmation of progressive disease ≤ 9 weeks prior to permanent discontinuation of study drug. The same assessment method and the same technique should be used on each patient while on study.

An end-of-treatment radiology assessment should be performed unless the patient already has radiographic confirmation of progressive disease ≤ 9 weeks prior to permanent discontinuation of study drug. The same assessment method and the same technique should be used on each patient while on study.

Overall tumor response and progression will be evaluated by the Investigator according to RECIST 1.1.

11 Pharmacokinetics

11.1 Pharmacokinetic Sampling

Blood samples for PK analysis of OBI-999 levels will be collected at the time points indicated in the Pharmacokinetic and ADA Sampling Schedules (see Table 9-2 [Part A] and Table 9-3 [Part B]). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

11.2 Pharmacokinetic Analytical Methodology

The concentrations of OBI-999 total antibody, ADC, and MMAE will be determined from the serum samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

Pharmacokinetic parameters will be calculated using a non-compartmental method from the PK samples collected during Cycles 1 and 2 and will include but will not be limited to C_{max}, AUC, elimination half-life ($t_{1/2}$), clearance (Cl), time to reach maximum concentration (T_{max}), and volume of distribution (V_d).

Pharmacokinetic methods may also be applied to further investigate OBI-999 exposure (e.g., accumulation of OBI-999, presence of dose- or time-dependent OBI-999 PK behavior, verification of influential factors on OBI-999 PK).

12 Safety Assessments

Safety assessments (vital signs, physical examinations, electrocardiogram [ECG] recording, AEs, ECOG, ophthalmology, clinical laboratory results [routine hematology, serum chemistry, coagulation, and urinalysis], and immunogenicity [ADAs]) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments, Table 9-1.

12.1 Vital Signs

Vital signs (body temperature, heart rate, systolic, and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 9-1). All vital signs will be measured after the patient has been resting for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Temperature measurement will be obtained as clinically indicated.

Body weight (without shoes) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.2 Physical Examination

A complete physical examination (head, eyes, ears, nose, throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at screening and early termination. Medical history will be recorded at screening, including smoking history, if applicable.

A limited physical examination to verify continued patient eligibility and to follow up any change in medical history will be performed at the visits indicated in the Schedule of Assessments (Table 9-1). Symptom-driven limited physical examinations will be performed as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Physical examinations 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.

As potential retinal and corneal findings were observed at the highest dose in the rat multiple dose toxicology study, ophthalmology examinations will be conducted as indicated in the Schedule of Assessments (Table 9-1) to document any treatment-emergent changes.

Medical history will include previous cancer therapies, cancer history, and past and ongoing concomitant illnesses.

12.3 Electrocardiogram

A 12-lead resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 9-1).

At screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

Additionally, a 12-lead resting ECG will be obtained in order to assess QTcF on Cycle 1 Day 1 prior to study drug infusion and on Cycle 1 Day 3 (48 ± 2 hours after the end of the study drug infusion on Day 1). If the QTcF increases above the upper limit of normal or if it increases on Day 3 more than 10 msec greater than at baseline, then repeat ECG testing for QTcF assessment should be performed prior to and 48 ± 2 hours after then next OBI-999 dose.

12.4 Laboratory Assessments

Laboratory assessment samples (Table 12-1) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 9-1).

Table 12-1 Laboratory Assessments

Hematology	**Serum chemistry**	**Urine analysis (dipstick)**
• Hemoglobin (Hb) • Hematocrit • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential	• Albumin • Alanine aminotransferase (ALT) • Alkaline phosphatase (ALP) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) or Urea • Bicarbonate • Creatinine • Creatine kinase • Electrolytes (Na, K, Cl, Ca, P, Mg) • Glucose • Lactate dehydrogenase (LDH) • Total bilirubin • Total protein • Uric acid	• Appearance • Blood • pH • Protein • Glucose • Ketones • Nitrite • Leukocyte esterase • Specific gravity • Urine human chorionic gonadotropin (HCG) (pre-menopausal females only) • Urobilinogen • Bilirubin • Microscopic, as needed
Coagulation	**Pregnancy test**	
• Prothrombin time (PT) • International Normalized Ratio (INR) • Activated partial thromboplastin time (aPTT)	To be performed on all female patients of child-bearing potential at the screening visit and early termination visit.	

Routine safety laboratory testing will be performed at the local laboratory following the laboratory's guidelines. Pharmacokinetic samples, ADAs, and biomarkers will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the Investigator and/or Sub-investigator. The signature and date can be wet ink or electronic. Any laboratory test results considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.5 Adverse Events

12.5.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study period or worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, incidence, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purpose of this study, treatment emergent AEs will be collected starting from the time the patient receives the first dose of study drug (from Cycle 1 Day 1) until 28 days after the last dose of study drug. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

Specific guidelines for classifying AEs by intensity (Grade) and relationship to study drug are given in Table 12-2 and Table 12-3. The severity of AEs will be graded according to the NCI CTCAE version 5.0 (Grades 1 to 5).

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted.

Table 12-2 Classification of Adverse Events by Intensity (NCI CTCAE Grade)

Mild (Grade 1): An event that is easily tolerated by the patient, causing minimal discomfort, and not interfering with everyday activities.
Moderate (Grade 2): An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3): An event that prevents normal everyday activities.
Life-threatening (Grade 4)
Death (Grade 5)

Table 12-3 Classification of Adverse Events by Relationship to Study Drug

Unrelated: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
Unlikely: This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.
Possibly: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the test drug.
Probably: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
Definitely: This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if re-challenge occurs); and (4) it follows a known pattern of response to the test drug.

12.5.2 Serious Adverse Events

An AE is considered "serious" if in the view of either the Investigator or Sponsor, it meets one or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE. Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.5.3 Serious Adverse Event Reporting

An SAE occurring during the study from the first dose of study treatment (Cycle 1 Day 1) to within 28 days of stopping the treatment must be reported to the contracted CRO and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator first becomes aware of the event. The Investigator must enter all SAE information into the electronic data capture (EDC) (preferred method), electronic mail (SAE Report Form), dedicated fax line or telephone line (emergency), to the Sponsor/contracted CRO.

If the Investigator contacts the contracted CRO by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the contracted CRO within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved or returns to the baseline condition.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.5.4 Pregnancy

Female patients of child-bearing potential must have a negative pregnancy test at the screening (serum) and the end of study/early termination visit (serum / urine). Following administration of study drug (from Cycle 1 Day 1 until 28 days after the last dose), any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a

completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, pregnancies should be considered important medical events and should be reported on the pregnancy report form/SAE form within 24 hours of the first learning of the event for further processing. The pregnancy will be categorized as a non-serious AE in the safety database for tracking purposes. The Investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event and the SAE reporting process will be followed.

12.5.5 Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.

12.6 ECOG Performance Status

ECOG performance status will be evaluated at the visits indicated in the Schedule of Assessments (Table 9-1). A summary of ECOG performance status is provided in Table 12-4.

Table 12-4 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

12.7 Immunogenicity

Safety assessment will also include evaluation of immunogenicity (i.e., ADAs). Immunogenicity assessments will be performed on Day 1 of Cycles 1-8, Cycle 12 and every 4 cycles thereafter, as well as end of study or early termination visit (Table 9-1).

If a patient is found to be ADA-positive at the end-of-study, the persistence of the ADA will be evaluated by collecting one more sample, 4 months later after the last study visit. The serum from each time point will test for anti-OBI-999 antibody concentration by a validated assay.

13 Exploratory Analyses

13.1 Tumor Tissue Samples

Tumor tissue biopsy or tissue samples will be collected at time of screening in both Part A and Part B of the study. Fresh (preferred) or archival tissue that is less than 10 years old is acceptable. Tumor tissue samples with fewer than 100 tumor cells will be deemed not evaluable. A fine needle aspirate, frozen sample, plastic embedded sample, bone, bone marrow, cell block, clot, cytologic specimen, decalcified sample, or formalin fixed sample that was frozen at any point prior to fixation will not be accepted. All attempts should be made to obtain fresh biopsy specimens. However, if historical sample is available, they should be retained along with histology/pathology report, if possible. All fresh biopsy specimens or historical samples should be sent to the qualified laboratory for testing. A minimum of 5 slides are required for the central laboratory Globo H assay for determination of eligibility for Part B. Up to 10 unstained additional slides should be provided, depending on availability, for testing tumor associated biomarkers as well as conducting a bridging study for the future companion diagnostic test.

The mandated baseline slides are to be used for Globo H testing by IHC to define the level and extent of Globo H expression, as this is the target of OBI-999. The 5 slides required for patients in Part B are part of the eligibility assessments, as all patients in Part B of the study must have a Globo H H-score of ≥ 100 to be eligible for study entry.

An analysis will be performed to determine whether there is a potential correlation between baseline tumor Globo H expression as assessed by IHC H-score and response to OBI-999 treatment, as assessed by change from baseline in the sum of diameters of measurable lesions and by RECIST response.

Apart from the mandatory Globo H assessments, up to 10 additional slides have been requested, if available, to identify potential predictive biomarkers for OBI-999 activity such as assessment of expression of additional tumor-associated glycans which may be pathologically associated with Globo H overexpression (e.g., SSEA-3 and SSEA-4) or molecular phenotypes of tumors which may be associated with aberrant Globo H expression.

14 Statistical Analysis

The Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details on the definitions of analysis populations, variables, and methodology in order to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using the SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Analyses will be conducted by dose level in Part A and by cancer type in Part B. Descriptive summaries for categorical variables will include counts and percentages. Descriptive

summaries for continuous variables will include means, medians, standard deviations, minimum, and maximum values. Categorical ordinal variables will be presented as a combination of class frequencies and percentages, together with mean and standard deviations of the ordinal scores. Descriptive summaries of time to event data will include medians and confidence intervals. Graphical summaries of the data may be presented. All data will be listed for all patients.

Further details of the analysis, including the handling of missing data, transformations, other data handling procedures, and analytical methodology will be provided in the SAP. Additional exploratory analyses of the data will be conducted as deemed appropriate.

14.1 Determination of Sample Size

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.

14.2 Analysis of Populations

The safety population to be analyzed will include all enrolled patients who receive at least 1 dose of study drug. The population used for analysis of clinical activity will be all enrolled patients who received at least one dose of study drug and had at least one follow-up tumor assessment scan.

14.3 Clinical Activity Analysis

ORR is defined as the percentage of patients with confirmed partial response (PR) or complete response (CR) based on tumor assessment as determined by RECIST 1.1. A confirmed response will be defined as two or more consecutive assessments separated by at least 3 weeks. 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.

CBR is defined as the percentage of patients with confirmed CR, PR, or stable disease. 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.

DOR is defined as time from date of reported confirmed PR or CR to the date of progression, and will be summarized descriptively using time-oriented summary statistics. Additionally, a listing of DOR for those patients experiencing response will be provided.

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 their last evaluable tumor assessment.

Kaplan Meier estimates and 95% confidence intervals will be presented for time-to-event endpoints such as PFS, if sufficient numbers of events to calculate meaningful statistics are observed.

14.4 Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated using a non-compartmental method from the PK samples collected during Cycles 1 and 2 and will include, but is not limited to C_{max}, AUC, $t_{1/2}$, Cl, T_{max}, and V_d.

To describe the dependency on dose, scatter plots of C_{max} and AUC versus dose will be provided. Summary statistics will be tabulated for the trough concentration (C_{min}) and peak concentrations (end of infusion) by dose and study day.

Pharmacometric methods may also be applied to further investigate OBI-999 and MMAE exposure (e.g., accumulation of OBI-999, presence of dose- or time-dependent OBI-999 PK behavior, verification of influential factors on OBI-999 PK).

14.5 Safety Analysis

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher and assessed for severity using NCI CTCAE version 5.0. Adverse events will be summarized by system organ class and preferred term and presented in decreasing order of incidence. Dose-limiting toxicities will also be summarized by dose and cohort. The incidence of TEAEs (events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. Serious adverse events and AEs causing discontinuation will be tabulated. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Vital signs, ECG data, ophthalmology, hematology, serum chemistry, coagulation, and urinalysis parameters from baseline and during study will be examined. Treatment-emergent changes in key laboratory parameters will be identified. Clinical laboratory data will be summarized for each time point that specimens are collected. Changes from baseline, for select clinical laboratory analytes may also be explored as specified in the SAP.

Summary tables will be provided for concomitant medications initiated prior to study enrollment or during the study period.

14.6 Safety Review Committee

The 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, adverse events, SAEs, clinical laboratory events, and dose modifications which will serve as the basis for their assessments.

14.7 Interim Analysis

There will not be a formal interim analysis; however, a description of the Dose Escalation Phase and the selection of the RP2D may be written up for the purposes of a manuscript.

15 Study Management

15.1 Approval and Consent

15.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with GCP guidelines.

15.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/ IEC. Approval is required for the study protocol, Investigator's Brochure (IB), protocol amendments, informed consent forms (ICFs), and patient information sheets.

15.1.3 Informed Consent

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Principal Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and International Conference on Harmonization (ICH) guidelines. The Principal

Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved ICF prior to the start of the study.

15.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. AEs will be coded using the MedDRA terminology.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are patient to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based EDC system. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of Data Clarification Forms (DCF). The eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

15.4 Record Retention

Study records and source documents must be preserved for at least 2 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

15.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

15.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and preliminary clinical activity profile data are adequate and well documented.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

15.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons for which they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority requirements is an Investigator responsibility.

15.8 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IRBs/IECs will review and approve this protocol and the ICF. All patients are required to give written informed consent prior to participation in the study.

15.9 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

15.10 Publication Policy and Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be patient to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, patient to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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17 Appendices

17.1 Appendix 1: Drug Preparation Instruction for OBI-999

1. OBI-999

- Dosage intravenous infusion: according to clinical protocol Section 8.2.
- Part A include dose levels of 0.4, 0.8, 1.2, 1.6, and 2.0 mg/kg (capping calculations at a maximum of 100 kg).
- Part B will include the Recommended Phase 2 dose of 1.2 mg/kg (capping calculations at a maximum of 100 kg).

2. Storage Condition:

- OBI-999 vials are to be stored at 2-8ºC.

3. Investigational Drugs:

- OBI-999 fill concentration and volume: 5 mg/mL, 5 mL in 10 mL transparent borosilicate type 1 glass vial.

  Contents: 5 mg/mL OBI-999 in 25 mM sodium citrate, 150 mM Arginine, pH 6.0, 0.02% Polysorbate 80.

At time of treatment, calculate the volume of OBI-999 DP needed according to the treatment dosage. Withdraw the volume from OBI-999 DP vial by using a sterile syringe and add the volume into an infusion bag containing 500 mL 0.9% saline or 5% glucose. Mix infusion bag by gently inverting the bag 4~5 times. **Do not shake the infusion bag vigorously**. After reconstitution, administer via intravenous infusion within 60±10 minutes.

The combined OBI-999 and infusion solution, 0.9% normal saline or 5% glucose. The administration of the drug must be completed within four hours after reconstitution to minimize potential microbial growth. If administration is not possible within four hours from reconstitution, the combined product should be destroyed according to the institutional pharmacy Standard Operating Procedure and documented in the drug accountability records.

The OBI-999 Drug Product (DP) should be administered to the study subjects within 4 hours of reconstitution at room temperature. Overall storage of the DP material should not exceed 8 hours at room temperature.

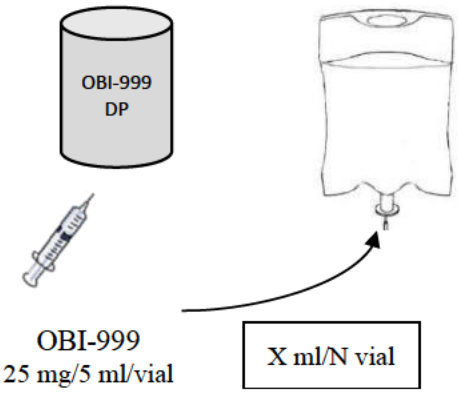
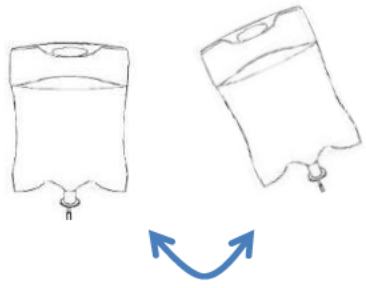
4. Illustration of Drug Preparation Procedures

OBI-999 Investigational Product Preparation Instruction Sheet

Determine the dose of OBI-999 DP.
Calculate the volume (X mL) of the OBI-999 DP solution needed by the following equation:

$$\textbf{X mL} = \frac{\text{Weight (Kg of Patient) x dose of OBI-999 (mg/kg)}}{\text{5 mg/mL}}$$

(Note: cap patient weight at 100 kg)

Description of Drug Preparation Procedures	**Illustration of Drug Preparation Procedures**
Step1. Withdraw the required amount of investigational product volume, **X mL**, from OBI-999 DP vial(s) using a syringe with minimum scale of 0.1 mL and add the OBI-999 DP into a **500 mL** 0.9% saline/5% glucose infusion bag.	
Step2. Mix the infusion bag by gently inverting the bag 4~5 times. **Note: Avoid vigorous shaking of the infusion bag.**	
Step3. OBI-999 investigational drug solution will be administered within **60±10 minutes**. **Note: Drug solution should be administered to the subjects within 4 hours of reconstitution at room temperature.**	 Intravenous infusion within 60±10 minutes

17.2 Appendix 2: Examples of Strong Inducers or Inhibitors of CYP3A

Strong Inhibitor of CYP3A	Strong Inducer of CYP3A
boceprevir	carbamazepine
clarithromycin	enzalutamide
cobicistat	mitotane
conivaptan	phenytoin
danoprevir and ritonavir	rifampin
diltiazem	St. John's wort[b]
elvitegravir and ritonavir	
grapefruit juice[a]	
idelalisib	
indinavir and ritonavir	
itraconazole	
ketoconazole	
lopinavir and ritonavir	
nefazodone	
nelfinavir	
paritaprevir, ritonavir, and (ombitasvir and/or dasabuvir)	
posaconazole	
ritonavir	
saquinavir and ritonavir	
telaprevir	
tipranavir and ritonavir	
troleandomycin	
voriconazole	

a. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
b. The effect of St. John's wort varies widely and is preparation-dependent
Source: Table 3-2 and Table 3-3 of https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

17.3 Appendix 3: Examples of Clinical Inhibitors of P-Glycoprotein

Inhibitor of P-Glycoprotein
amiodarone
carvedilol
clarithromycin
dronedarone
itraconazole
lapatinib
lopinavir and ritonavir
propafenone
quinidine
ranolazine
ritonavir
saquinavir and ritonavir
telaprevir
tipranavir and ritonavir
verapamil

Source: Table 5-2 of https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-2