A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

ISN/Protocol 8951-CL-0301

Spotlight

Version 5.0

Incorporating Substantial Amendment 4 [See Section 13]

18 Oct 2021

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EudraCT 2017-002567-17

Sponsor:

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way
Northbrook, IL 60062

Protocol History:

Version 1.0 [31 Jan 2018]
Version 2.0 [06 Jul 2018] Incorporating Substantial Amendment 1
Version 3.0 [06 Aug 2019] Incorporating Substantial Amendment 2
Version 3.1 [06 Jan 2021] Incorporating Nonsubstantial Amendment 1
Version 4.0 [29 Aug 2019] Incorporating Country-specific Substanial Amendment 3 for China
Version 4.1 [11 Jan 2021] Incorporating Country-specific Nonsubstantial Amendment 2 for China

Table of Contents

I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors and contributors, etc.) are located in [Section 15 Sponsor's Signatures].

2. COORDINATING INVESTIGATOR'S SIGNATURE (Optional)

The Coordinating Investigator's signature, where applicable, can be found in [Section 14 Coordinating Investigator's Signature]; located at the end of this document.

3. INVESTIGATOR'S SIGNATURE

A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

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Version 5.0 Incorporating Substantial Amendment 4

18 Oct 2021

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ----------
<Insert name and qualification of the Investigator>

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** Astellas Pharma Global Development, Inc. Global Pharmacovigilance **North America Fax number**: +1-888-396-3750 North America Alternate Fax number: +1-847-317-1241 **International Fax Number** : +44-800-471-5263 **Email: safety-us@astellas.com** **Japan investigational sites:** PAREXEL International Global Monitoring Operations Fax: 03-6888-2947
Medical Monitor/Study Physician:	PPD Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, Illinois 60062 PPD
Clinical Research Contacts:	PPD Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, Illinois 60062 PPD
Clinical Research Contacts Japan:	Corporate Name: Astellas Pharma Inc. Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
5-FU	fluorouracil
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (GPT)
ANC	absolute neutrophil count
APEBV	Astellas Pharma Europe B.V.
AST	aspartate aminotransferase (GOT)
βhCG	beta human chorionic gonadotropin (hCG)
C1D1	Cycle 1 Day 1
CA	Competent Authorities
CDC	complement-dependent cytotoxicity
CI	confidence interval
CLDN	claudin
C_{max}	maximum concentration
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria For Adverse Events
DCR	disease control rate
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase deficiency
ECG	electrocardiogram
ECL	electrochemiluminescense
eCOA	Electronic Clinical Outcomes Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
EORTC	European Organization for Research and Treatment of Cancer
EOX	epirubicin, oxaliplatin and capecitabine
EQ-5D	EuroQOL Five Dimensions Questionnaire
EQ5D-5L	EuroQOL Five Dimensions Questionnaire 5L
EU	European Union
FAS	full analysis set
FIM	first-in-human
FFPE	formalin-fixed paraffin embedded
GCP	Good Clinical Practices

Abbreviations	Description of abbreviations
GE	gastroesophageal
GEJ	gastroesophageal junction
GHS/QoL	Global Health Status/Quality of Life
GMP	Good Manufacturing Practices
GP	Global Pain
Hgb	hemoglobin
HEOR	health economics and outcomes research
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRU	Health Resource Utilization
HSR	hypersensitivity reactions
IB	Investigator's Brochure
ICF	informed consent form
ICH	international council for harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	independent data monitoring committee
IEC	independent ethics committee
IHC	immunohistochemistry
IMAB	ideal monoclonal antibody
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IRT	interactive response technology
ISN	international study number
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous, intravenously
LA-CRF	liver abnormality case report form
LFT	liver function tests
mAbs	monoclonal antibodies
MCH	mean corpuscular hemoglobin
mFOLFOX6	5-fluorouracil, folinic acid and oxaliplatin
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drugs
OG25-Pain	oesophago-gastric questionnaire (OG25) on abdominal pain and discomfort
ORR	objective response rate

Abbreviations	Description of abbreviations
OS	overall survival
PD	progressive disease
PF	physical function
PFS	progression free survival
PFS2	progression free survival following second-line anticancer treatment
PGx	pharmacogenomics
PKAS	pharmacokinetic analysis set
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
PTL	platelet count
QLQ-C30	Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30)
QLQ-OG25	Quality of Life Questionnaire - Oesophago-Gastric Module 25 (OG-25)
QTc	QT corrected
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
(S)AE	serious adverse event and/or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SOP	standard operating procedure
SPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reactions
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
TTCD	time to confirmed deterioration
TTP	time to progression
ULN	upper limit of normal
USM	urgent safety measure
VEGF	vascular endothelial growth factor
WBC	white blood cell
WOCBP	woman of childbearing potential

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a trial before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a trial.
Enroll	To register or enter a subject into a clinical trial. NOTE: Once a subject has received the study drug or placebo, the clinical trial protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Study treatment	Includes zolbetuximab/placebo and all components of mFOLFOX6
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version No of Protocol Synopsis:	18 Oct 2021, Version 5.0
Sponsor: Astellas Pharma Global Development, Inc. (APGD)	**Protocol Number:** 8951-CL-0301
Name of Study Drug: zolbetuximab (IMAB362)	**Phase of Development:** Phase 3
Title of Study: A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma	
Planned Study Period: From 2Q2018 to 2Q2023	

Study Objective(s)**:**

Primary

- To evaluate the efficacy of zolbetuximab plus mFOLFOX6 compared with placebo plus mFOLFOX6 (as first-line treatment) as measured by Progression Free Survival (PFS) in subjects with Claudin (CLDN)18.2 positive, human epidermal growth factor receptor 2 (HER2)–negative locally advanced unresectable or metastatic gastric and gastroesophageal junction (GEJ) adenocarcinoma

Secondary

- To evaluate efficacy as measured by Overall Survival (OS) as a key secondary objective
- To evaluate the physical function (PF), OG25-Pain and GHS/QoL scores as measured by European Organization for Research and Treatment of Cancer (EORTC) as a key secondary objective
- To evaluate efficacy as measured by Objective Response Rate (ORR)
- To evaluate efficacy as measured by Duration of Response (DOR)
- To evaluate safety and tolerability of zolbetuximab
- To further evaluate other health related quality of life (HRQoL) using additional parameters as measured by EORTC QLQ-C30, QLQ-OG25, Global Pain (GP) and the EuroQOL Five Dimensions Questionnaire 5L (EQ5D-5L) questionnaires
- To evaluate the pharmacokinetics of zolbetuximab
- To evaluate the immunogenicity profile of zolbetuximab

Exploratory

- To evaluate efficacy as measured by Time to Progression (TTP)
- To evaluate PFS following subsequent anticancer treatment (PFS2)
- To evaluate Disease Control Rate (DCR)
- To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome to zolbetuximab and mFOLFOX6.
- To evaluate Health Resource Utilization (HRU)

Planned Total Number of Study Centers and Location(s):
Approximately 240 centers globally

Study Population:
Subjects with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumors are CLDN18.2 positive, HER2-negative and who have not been previously treated for metastatic disease with chemotherapy (1st line).
For the purpose of this study, CLDN18.2-positive is defined as CLDN18.2 expression in ≥ 75% of tumor cells demonstrating moderate to strong membranous staining as determined by central immunohistochemistry (IHC) testing.

Number of Subjects to be Enrolled/Randomized:
Approximately 550 subjects

Study Design Overview:
This global, multi-center, double-blind, 1:1 randomized, phase 3 study will evaluate efficacy of zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6 as first-line treatment in subjects with CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma.
PFS is the primary outcome. Secondary outcomes include OS, ORR, DOR, safety and tolerability, HRQoL, pharmacokinetics and the immunogenicity profile of zolbetuximab. Exploratory outcomes include TTP, PFS2, DCR biomarkers, and HRU.
Approximately 550 subjects will be 1:1 randomized into 1 of 2 treatment arms:

- Arm A (mFOLFOX6 chemotherapy in combination with zolbetuximab)
- Arm B (mFOLFOX6 chemotherapy in combination with placebo)

Randomization of subjects will be stratified by the following factors:

- Region (Asia vs Non-Asia)
- Number of organs with metastatic sites (0 to 2 vs ≥ 3)
- Prior gastrectomy (Yes or No)

Screening:

The Screening period is 45 days from full main informed consent form (ICF) signature. Retesting of lab values is allowed within the 45-day Screening period. Re-screening outside the 45-day window under a new subject number may be allowed once and upon discussion with the Medical Monitor. Computerized tomography (CT) scans and magnetic resonance imaging (MRI) conducted as part of a subject's routine clinical management (i.e., standard of care) obtained before signing the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the Screening period.
Formalin fixed paraffin embedded (FFPE) tumor tissue will be collected for central testing to determine CLDN18.2 and HER2 status.
An optional partial screening ICF may be available to allow central testing of tissue for CLDN18.2 and HER2 only.

- Archival tumor tissue is preferred.
    - A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum* of 15 FFPE unstained slides are required, as allowed per local policy. If slides are submitted, the slides should be freshly cut from the FFPE block within the time frame described in the laboratory manual.
    - If local HER2 results are already available from local testing, a minimum* of 12 FFPE unstained slides are required to be submitted to the central laboratory, as allowed per local policy.

      *If the required minimum number of slides is not able to be submitted, sponsor notification and approval is required.

- If the specimen is insufficient or unavailable, a biopsy may be performed to obtain tumor sample.
    - Sponsor pre-approval is required when the sole purpose of the biopsy procedure is to assess eligibility for this study.
    - If the required number of slides cannot be provided, the sponsor or designee should be contacted for further guidance.

Treatment Period:

Subjects will be treated with either zolbetuximab (Arm A) or placebo (Arm B) on Days 1 and 22 starting at C1D1 until the subject meets study treatment discontinuation criteria.

Subjects will also receive up to 12 treatments of mFOLFOX6 (or components of mFOLFOX6 if some components are discontinued due to toxicity) over 4 or more cycles (each cycle is approximately 42 days) in which mFOLFOX6 is administered on Days 1, 15 and 29 of each cycle. After 12 mFOLFOX6 treatments, subjects may continue to receive fluorouracil (5-FU) and folinic acid on Days 1, 15 and 29 of each cycle at the investigator's discretion until the subject meets study treatment discontinuation criteria. (NOTE: An ECG is required to be performed and assessed locally prior to every oxaliplatin infusion [before any antiemetic treatment] and following completion of every oxaliplatin infusion. ECG should be performed up to 48 hours *prior* to and up to 6 hours *following* every oxaliplatin infusion. Oxaliplatin administration and electrolyte levels should be managed according to the investigator's judgement for subjects with grade 1 or 2 hypokalemia, hypomagnesemia and/or hypocalcemia.)

If a subject discontinues mFOLFOX6 (or components of mFOLFOX6) due to any reason other than disease progression as confirmed by independent review committee (IRC), they may continue on zolbetuximab/placebo at the discretion of the investigator provided that all of the following have been met:

- the subject completed at least 1 cycle (42 days) of mFOLFOX6 treatment;
- the subject will not receive another systemic chemotherapy, immunotherapy, radiotherapy or other treatment intended for antitumor activity; and
- in the investigator's opinion the subject continues to derive clinical benefit with acceptable toxicity.

Subjects should continue to follow the Study Treatment Period Schedule of Assessments [Table 1].

Safety Assessments

Safety will be evaluated based on adverse events (AEs), vital signs, electrocardiograms (ECGs), physical exams, Eastern Cooperative Oncology Group (ECOG) performance status and laboratory assessments. Severity of AEs and laboratory abnormalities will be assessed based on Common Terminology Criteria For Adverse Events (CTCAE) v4.03.

Radiologic Imaging and Independent Review Committee:

Radiologic imaging will be evaluated at Screening (within 28 days prior to randomization) and every 9 weeks (± 7 days) counting from C1D1 for the first 54 weeks and then every 12 weeks (± 7 days) thereafter until subject develops radiological disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by IRC or starts other systemic anticancer treatment, whichever comes earlier.

All radiologically evaluable disease (measurable and/or non-measurable), per local assessment, must be documented at Screening and re-assessed at each subsequent radiologic evaluation. Imaging will include CT scans with contrast of the thorax, abdomen, and pelvis. If CT scan with contrast is medically not feasible, magnetic resonance imaging may be used for imaging. Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease in bone or brain is suspected, respectively. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change. For randomized subjects, screening imaging should be

sent to the central imaging vendor no later than at the time of submission of the first on-treatment imaging. All imaging acquired post randomization will be sent to the central imaging vendor within 7 days of scanning for the blinded independent central assessment of radiological tumor response based on RECIST 1.1 [Eisenhauer et al, 2009]. The investigator should make every effort to immediately submit radiologic assessments for IRC review when progressive disease (PD) is suspected.

Study Treatment Discontinuation and Safety Follow-up Visits

Following discontinuation from zolbetuximab/placebo, subjects will have a zolbetuximab/placebo Study Treatment Discontinuation Visit, and 30-day and 90-day Safety Follow-up Visits following their last dose of zolbetuximab/placebo.

Additionally, if mFOLFOX6 (all components) is discontinued on a different day than zolbetuximab/placebo, subjects will also have a Study Treatment Discontinuation Visit, and 30-day and 90-day Safety Follow-up Visits following the last dose of mFOLFOX6 (all components). The mFOLFOX6 30-day and 90-day Safety Follow-up Visits may be conducted by telephone if the subject is unable to visit the study site and will require only contact for AE/SAE collection.

Post-Treatment Follow-up Period (for PFS):

If a subject discontinues all study treatments (zolbetuximab/placebo and all components of mFOLFOX6) prior to IRC-confirmed radiological disease progression, the subject will enter the Post-Treatment Follow-up Period and continue to undergo scheduled imaging assessments every 9 weeks (or every 12 weeks if subjects has been on study over 54 weeks) until radiologic disease progression (i.e., PFS event) or the subject starts any other anticancer treatment, whichever occurs earlier.

If study treatment (zolbetuximab/placebo and all components of mFOLFOX6) is discontinued due to disease progression (PFS event), the subject will enter the Long Term and Survival Follow-up Period.

Long Term Follow-up Period (for PFS2) and Survival Follow-up (for OS) Period:

Following disease progression on first-line treatment or start of any other anticancer treatment, subjects will be followed in the Long-Term and Survival Follow-up Period per institutional guidelines, but not less frequently than every 12 weeks to confirm survival status (i.e. OS) and collect subsequent anticancer treatment details and progression status until PD following subsequent anticancer therapy (PFS2) is documented or the subject starts another systemic anticancer treatment , whichever occurs earlier. Radiologic imaging for PFS2 will be done per standard of care and read locally. Survival Follow-up Period will continue until death (from any cause).

All post-progression details, including subsequent anticancer treatment and date and site of progression, will be recorded on the electronic case report form (eCRF). Subject contact by phone or other remote methods is sufficient during Long Team and Survival Follow-up. Additional follow-up contacts may be required per sponsor request for analysis purposes.

Biomarkers and Other Sampling

Samples for pharmacokinetics, immunogenicity and biomarkers, as well as FFPE tumor tissue specimens (for eligibility) will be collected. Optional pharmacogenomics and post-progression tumor samples may be collected for those subjects who sign a separate ICF.

Electronic Clinical Outcomes Assessments (HRQoL and HRU)

HRQoL and HRU should be assessed during the visit (or up to 48 hours) before any antiemetic or drug treatment(s) administration and before the disease status is discussed with the subject. Assessments will be collected at Screening (except HRU), every 3 weeks, at study treatment

discontinuation and 30 and 90 days post zolbetuximab/placebo treatment. HRQoL will be measured by EORTC QLQ-C30, QLQ-OG25, GP and the EQ5D-5L.

Independent Data Monitoring Committee and Independent Data Analysis Center

An Independent Data Monitoring Committee (IDMC) will be established and will monitor the benefit-risk of study treatment in an unblinded fashion per pre-defined IDMC charter. The first IDMC meeting will be approximately 6 weeks after the 40th subject enrolled has completed or discontinued Cycle 1 (6 weeks) and meetings will be conducted regularly thereafter, as determined by the IDMC.

An Independent Data Analysis Center will conduct an interim analysis of OS at the same time as the final PFS analysis, which will occur when approximately 300 PFS events have occurred. This analysis will be utilized by the IDMC to recommend whether the study should be stopped earlier than planned if zolbetuximab in combination with mFOLFOX6 has a favorable outcome compared with mFOLFOX6 in combination with placebo. If the OS interim analysis demonstrates a highly more favorable outcome for zolbetuximab in combination with mFOLFOX6, the study may be stopped for success. However, any subject continuing to derive clinical benefit from zolbetuximab/placebo in combination with mFOLFOX6 as assessed by the investigator will be allowed to continue treatment. The full procedures for IDMC review will be described in a separate IDMC charter.

Inclusion/Exclusion Criteria:

Inclusion Criteria*:*

Waivers to the inclusion criteria will **NOT** be allowed.

General Criteria:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject or legally authorized representative (if applicable) prior to any study-related procedures.
2. Subject is considered an adult (e.g., ≥ 18 years of age in the US) according to local regulation at the time of signing the informed consent.
3. Subject agrees not to participate in another interventional study while on study treatment.
4. A female subject is eligible to participate if she is not pregnant (negative serum pregnancy test at Screening; female subjects with elevated serum beta human chorionic gonadotropin (βhCG) and a demonstrated non-pregnant status through additional testing are eligible) and at least 1 of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 12.3 Contraception Requirements
    OR
    b. WOCBP who agrees to follow the contraceptive guidance as defined in Appendix 12.3 Contraception Requirements throughout the treatment period and for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs.
5. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 6 months after the final study treatment administration.
6. Female subject must not donate ova starting at Screening and throughout the study period, and for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs.
7. A sexually active male subject with female partner(s) who are of childbearing potential must agree to use contraception as detailed in Appendix 12.3 Contraception Requirements during the treatment period and for at least 6 months after the final study drug administration.

8. Male subject must not donate sperm starting at Screening and throughout the study period and for 6 months after the final study drug administration.
9. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or for the time partner is breastfeeding throughout the study period and for 6 months after the final study drug administration.

Disease Specific Criteria:

10. Subject has histologically confirmed diagnosis of Gastric or GEJ adenocarcinoma.
11. Subject has radiologically confirmed locally advanced unresectable or metastatic disease within 28 days prior to randomization.
12. Subject has radiologically evaluable disease (measurable and/or non-measurable disease according to RECIST 1.1), per local assessment, ≤ 28 days prior to randomization. For subjects with only 1 evaluable lesion and prior radiotherapy ≤ 3 months before randomization, the lesion must either be outside the field of prior radiotherapy or have documented progression following radiation therapy.
13. Subject's tumor expresses CLDN18.2 in ≥ 75% of tumor cells demonstrating moderate to strong membranous staining as determined by central IHC testing.
14. Subject has a HER2-Negative tumor as determined by local or central testing on a gastric or GEJ tumor specimen.

Physical or Laboratory Findings

15. Subject has ECOG performance status 0 to 1.
16. Subject has predicted life expectancy ≥ 12 weeks in the opinion of the investigator.
17. Subject must meet all of the following criteria based on the centrally or locally analyzed laboratory tests collected within 14 days prior to randomization. In the case of multiple sample collections within this period, the most recent sample collection with available results should be used to determine eligibility.
    a. Hemoglobin (Hgb) ≥ 9 g/dL. Subjects requiring transfusions are eligible if they have a post-transfusion Hgb ≥ 9 g/dL.
    b. Absolute neutrophil count ≥ 1.5 x 10^9/L
    c. Platelets ≥ 100 x 10^9/L
    d. Albumin ≥ 2.5 g/dL
    e. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) without liver metastases (or < 3.0 x ULN if liver metastases are present)
    f. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x ULN without liver metastases (or ≤ 5 x ULN if liver metastases are present)
    g. Estimated creatinine clearance ≥ 30 mL/min
    h. Prothrombin time/international normalized ratio and partial thromboplastin time ≤ 1.5 x ULN (except for subjects receiving anticoagulation therapy)

Exclusion Criteria:

Waivers to the exclusion criteria will **NOT** be allowed.

Subject who meets any of the following exclusion criteria prior to enrollment is not eligible for enrollment:

Prohibited Treatment or Therapies

1. Subject has received prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. However, subject may have received either neo-adjuvant or adjuvant chemotherapy, immunotherapy or other systemic anticancer therapies as long as it was completed at least 6 months prior to randomization. Subject may have received treatment with herbal medications that have known antitumor activity > 28 days prior to randomization.
2. Subject has received radiotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma ≤ 14 days prior to randomization and has not recovered from any related toxicity.
3. Subject has received systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to randomization. Subjects using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone), receiving a single dose of systemic corticosteroids or receiving systemic corticosteroids as premedication for radiologic imaging contrast use are allowed.
4. Subject has received other investigational agents or devices within 28 days prior to randomization.

Medical History or Concurrent Disease

5. Subject has prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanized or chimeric antibodies.
6. Subject has known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment.
7. Subject has prior severe allergic reaction or intolerance to any component of mFOLFOX6.
8. Subject has known dihydropyrimidine dehydrogenase deficiency (DPD). (NOTE: Screening for DPD deficiency should be conducted per local requirements.)
9. Subject has a complete gastric outlet syndrome or a partial gastric outlet syndrome with persistent/recurrent vomiting.
10. Per investigator judgement, subject has significant gastric bleeding and/or untreated gastric ulcers that exclude the subject from participation.
11. Subject has a known history of a positive test for human immunodeficiency virus (HIV) infection or known active hepatitis B (positive HBs Ag) or C infection. NOTE: Screening for these infections should be conducted per local requirements.
    a. For subjects who are negative for HBs Ag, but HBc Ab positive, an HB DNA test will be performed and if positive, the subject will be excluded.
    b. Subjects with positive hepatitis C virus (HCV) serology, but negative HCV RNA test are eligible.
    c. Subjects treated with HCV with undetectable viral load results are eligible.
12. Subject has an active autoimmune disease that has required systemic treatment within the past 3 months prior to randomization.
13. Subject has active infection requiring systemic therapy that has not completely resolved within 7 days prior to randomization.

14. Subject has significant cardiovascular disease, including any of the following:
    a. Congestive heart failure (defined as New York Heart Association Class III or IV), myocardial infarction, unstable angina, coronary angioplasty, stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis within 6 months prior to randomization.
    b. History of clinically significant ventricular arrhythmias (i.e., sustained ventricular tachycardia, ventricular fibrillation or Torsades de Pointes
    c. QTc interval > 450 msec for male subjects: QTc interval > 470 msec for female subjects
    d. History or family history of congenital long QT syndrome
    e. Cardiac arrhythmias requiring anti-arrhythmic medications (Subject with rate controlled atrial fibrillation for > 1 month prior to randomization are eligible).
15. Subject has a history of central nervous system metastases and/or carcinomatous meningitis from gastric/GEJ cancer.
16. Subject has known peripheral sensory neuropathy > grade 1 unless the absence of deep tendon reflexes is the sole neurological abnormality.
17. Subject has had a major surgical procedure ≤ 28 days prior to randomization.
    a. Subject is without complete recovery from a major surgical procedure ≤ 14 days prior to randomization.
18. Subject has psychiatric illness or social situations that would preclude study compliance, per investigator judgement.
19. Subject has another malignancy for which treatment is required per investigator's clinical judgement.
20. Subject has any concurrent disease, infection or comorbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.

Investigational Product(s):

zolbetuximab/ placebo:	zolbetuximab: the investigational product, zolbetuximab, is a sterile lyophilized powder preparation with the chimeric monoclonal antibody zolbetuximab as the active pharmaceutical ingredient. Each vial contains 105 mg of zolbetuximab and has to be reconstituted with 5.0 mL sterile water for injection, to a concentration of 20 mg/mL. Further dilution with sterile 0.9% Sodium Chloride Injection, to a final concentration of 2 mg/mL is required. Placebo: Placebo will not be manufactured or provided by the Sponsor. 0.9% Sodium Chloride Injection will be used for placebo treatment arm as a placebo infusion solution.
Dose(s):	800 mg/m² loading dose of zolbetuximab at C1D1 followed by subsequent doses of 600 mg/m² every 3 weeks.
Dosing Schedule:	Subjects will be treated with either zolbetuximab (Arm A) or placebo (Arm B) on Days 1 and 22 in each cycle (each cycle is approximately 42 days) starting at C1D1 until the subject meets study treatment discontinuation criteria. Zolbetuximab/placebo should be administered after anti-emetic premedication but prior to mFOLFOX6 (on visits when both are to be administered on the same day; e.g., C1D1).
Mode of Administration:	Intravenous (IV) infusion of zolbetuximab/placebo as a minimum 2-hour infusion. IV infusion may be interrupted or slowed down to manage toxicity. **Please refer to the Pharmacy Manual and Infusion Guidelines for more detailed information.**

Other Product(s)

0.9% Sodium Chloride Injection	0.9% Sodium Chloride Injection will be used for infusion solution in this study for both zolbetuximab arm and placebo arm. Details of preparation of infusion solution are provided in the Pharmacy Manual and Infusion Guidelines ***SPECIFIC TO JAPAN:*** In this study, 0.9% Sodium Chloride Injection is not considered an 'investigational product' as defined in J-GCP.
mFOLFOX6:	Subjects will receive up to 12 treatments of mFOLFOX6 (or components of mFOLFOX6 if some components are discontinued due to toxicity) over 4 or more cycles (each cycle is approximately 42 days) in which mFOLFOX6 is administered on Days 1, 15 and 29. After 12 treatments, subjects may continue to receive 5-FU and folinic acid at the investigator's discretion until the subject meets study treatment discontinuation criteria. mFOLFOX6 (or components) are to be administered <u>after</u> zolbetuximab/placebo on visits when both treatments are to be administered on the same day (e.g., C1D1, C2D1, etc.).
Oxaliplatin:	85 mg/m^2 IV infusion over 2 hours or longer per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle), for a maximum of 12 doses. (NOTE: ECG is required to be performed and assessed locally prior to every oxaliplatin infusion [before any antiemetic treatment] and following completion of every oxaliplatin infusion. ECG should be performed up to 48 hours *prior* to and up to 6 hours *following* every oxaliplatin infusion. Oxaliplatin administration and electrolyte levels should be managed according to the investigator's judgement for subjects with grade 1 or 2 hypokalemia, hypomagnesemia and/or hypocalcemia.
Folinic Acid (Leucovorin or local equivalent):	Leucovorin: 400 mg/m^2 IV infusion over 2 hours or longer per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle). Leucovorin can be continued beyond 4 cycles based on investigator's judgement. ***SPECIFIC TO JAPAN:*** Or, levofolinate 200 mg/m^2 IV infusion over 2 hours or longer per institutional standard of care every 2 weeks for 4 cycles. Levofolinate can be continued beyond 4 cycles based on investigator's judgement.) Or, levo-folinic acid may be given as deemed appropriate by the investigator in accordance with institutional standard of care.
5-FU Bolus:	400 mg/m^2 IV bolus over 5 to 15 minutes or per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle). 5-FU can be continued beyond 4 cycles based on investigator's judgement.
5-FU Infusion:	2400 mg/m^2 IV infusion over 46 to 48 hours or per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle). 5-FU can be continued beyond 4 cycles based on investigator's judgement.

Antiemetic Pre-medications	Antiemetic premedication (prophylactic antiemetics) should be administered prior to each study treatment.
	(NOTE: Subjects receiving zolbetuximab do not need to be premedicated for prevention of IRRs; however, subjects should be closely monitored for IRRs to facilitate early identification and management.)
	• Antiemetic premedication
	  o IV antiemetic premedication should be initiated prior to treatment, or
	  o Oral antiemetic premedication should be initiated at a minimum of 30 minutes prior to treatment.
	• On days when zolbetuximab/placebo and mFOLFOX6 are administered together, antiemetic premedication should be given prior to zolbetuximab/placebo administration.
	• It is recommended that the prophylactic antiemetic regimen include (but is not limited to) the following agents:
	  o NK-1 receptor blockers
	  o 5-HT3 receptor blockers*
	* To minimize the risk of Torsades de Pointes, administer 5-HT3 receptor blockers with caution to subjects who have or may develop QTc prolongation.
	Antiemetic premedication should be administered according to institutional standard of care, published guidelines and the respective product package insert(s).
	Corticosteroids:
	• The impact of corticosteroids on the potential efficacy of zolbetuximab is not known. Therefore, consideration should be given to avoid or minimize the use of corticosteroids as a prophylactic antiemetic, if possible.
	• For a subject's first dose of zolbetuximab/placebo, it is recommended that the prophylactic use of corticosteroids be avoided.

Concomitant Medication Restrictions or Requirements:

Prohibited Concomitant Treatment

The following are strictly prohibited:

- Sorivudine or analogs (during 5-FU treatment)
- Concurrent non-steroid systemic immunosuppressive agents, (for systemic corticosteroids see cautionary concomitant treatment below).
- Live vaccines should be avoided during the treatment period in which subject is receiving oxaliplatin or 5-FU and up to 6 months after final oxaliplatin or 5-FU dose. In cases where a live vaccine is needed for COVID-19 prevention and allowed per local regulations, please contact the Medical Monitor for discussion.
- Other systemic chemotherapy, immunotherapy, radiotherapy, herbal medications or other treatments intended for antitumor activity.
  - Palliative radiotherapy for peripheral bone metastases is allowed.
  - For gastric bleeding, palliative radiotherapy is prohibited, but esophagogastroduodenoscopy with epinephrine injection is allowed.
- Investigational products or therapy other than zolbetuximab.

Cautionary Concomitant Treatment

Considerations should be given to avoid or minimize the use of the following concomitant medications, if possible, during zolbetuximab/placebo treatment:

- Systemic corticosteroids, because of their impact on the potential efficacy of zolbetuximab is not known.
    - Systemic corticosteroids should be avoided or minimized while subject is on study treatment unless required for management of an emergent medical condition (e.g., severe nausea/vomiting or hypersensitivity reaction).
    - For a Subject's first dose of zolbetuximab/placebo, it is recommended that the prophylactic use of corticosteroids be avoided.
    - Inhaled, intranasal, ophthalmic, otic and topically applied steroids are allowed.
    - Subjects are allowed to use a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg/day of hydrocortisone or up to 10 mg/day of prednisone), receive a single dose of systemic corticosteroids or receive systemic corticosteroids as premedication for radiologic imaging contrast use.
- Administer 5-HT3 blockers with caution in subjects who have or may develop QTc prolongation.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) because of the potential to cause gastric ulcers and covert bleeding.
    - In such cases where NSAID use is necessary, the use of NSAIDs with lower gastric ulcerogenic potential is preferred and concomitant gastric protection with proton pump inhibitors is recommended.

The following should be avoided or used with caution during 5-FU treatment and appropriate monitoring should be conducted:

- CYP2C9 substrates
- Metronidazole and cimetidine
- Anti-epileptic medications (e.g., phenobarbital, phenytoin and primidone)

The following should be avoided or used with caution during oxaliplatin treatment and appropriate monitoring should be conducted:

- Medications known to prolong the QT or QTc interval (refer to https://www.crediblemeds.org for a list of these medications)

Duration of Treatment:

Subjects will receive zolbetuximab/placebo until IRC confirmed disease progression, toxicity requiring study treatment cessation, start of another anticancer treatment or other treatment discontinuation criteria are met.

Subjects will also receive up to 12 treatments (4 or more cycles) of mFOLFOX6 (or some of its components) followed by continued use of folinic acid and 5-FU (based on investigator's judgement) beyond 12 treatments until study treatment discontinuation criteria are met.

Study Treatment Discontinuation Criteria

A subject who enrolled in the study and for whom study treatment (zolbetuximab/placebo and all components mFOLFOX6) is permanently discontinued for any reason will be assessed as having met study treatment discontinuation criteria.

As survival is the secondary end-point of the study, all subjects will be followed for survival after meeting study treatment discontinuation criteria unless the subject withdraws consent or is considered lost to follow-up after repeated attempts to contact or if the sponsor discontinues the study.

A subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

A subject will be discontinued from study treatment (zolbetuximab/placebo and all components mFOLFOX6) if any of the following occur:

- Investigator determines it is in the subject's best interest to discontinue study treatment
- Subject develops radiological disease progression per RECIST 1.1 criteria based on assessment by IRC.
    - If the investigator believes, that the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study treatment until an additional radiologic assessment is completed (≤ 9 weeks from previous radiologic assessment).
        - If the additional radiologic assessment by IRC indicates PD per RECIST 1.1 then the subject must be discontinued from study treatment.
        - If the additional radiologic assessment by IRC does not confirm the initial assessment of PD, the subject may continue study treatment.
- Subject develops clinical progression per investigator assessment and radiologic assessment is not medically feasible to confirm radiologic progression due to the subject's condition.
- Subject starts another systemic chemotherapy, immunotherapy, radiotherapy or other treatment intended for antitumor activity.
- Subject starts another investigational agent or device
- Subject develops unacceptable toxicity.
- Subject has a delay of study treatment (zolbetuximab/placebo and all components mFOLFOX6) for > 28 days from when the next study treatment was scheduled to be administered (> 49 days from when the last dose of zolbetuximab/placebo and > 42 days from when the last dose of mFOLFOX6 began).
- Subject develops inter-current illness that the investigator determines may jeopardize the subject's safety if the subject continues to receive study treatment.
- Female subject becomes pregnant.
- Significant deviation from the protocol or eligibility criteria as determined by the sponsor.
- Subject declines further treatment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject is noncompliant with the protocol based on investigator or Medical Monitor assessment.

Note: If a subject discontinues mFOLFOX6 and zolbetuximab/placebo due to any reason other than IRC confirmed disease progression (and is not receiving any other anticancer therapy), the subject must be followed according to the protocol-specified radiologic assessment schedule until radiological disease progression per RECIST 1.1 criteria is confirmed by IRC assessment.

Study Discontinuation Criteria

All subjects should remain in the study through the Survival Follow-up Period, (OS is a key secondary study endpoint). A subject will be discontinued from the Post-Treatment, Long Term and Survival Follow-up Periods if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death (from any cause)
- Study termination by the sponsor

Endpoints for Evaluation:

Primary:

- PFS, defined as the time from the date of randomization until the date of radiological PD (per RECIST 1.1 by IRC) or death from any cause, whichever is earliest

Secondary:

- OS, defined as the time from the date of randomization until the date of death from any cause
- Time to confirmed deterioration (TTCD) using the PF, OG25-Pain and GHS/QoL scores as measured by EORTC QLQ-C30 and QLQ-OG25. TTCD is defined as time to first confirmed deterioration, i.e., time from randomization to first clinically meaningful deterioration that is confirmed at the next scheduled visit.
- ORR, defined as the proportion of subjects who have a best overall response (BOR) of CR or PR as assessed by IRC per RECIST 1.1
- DOR, defined as the time from the date of the first response (CR/PR) until the date of PD as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest
- Safety and tolerability, as measured by AEs, laboratory test results, vital signs, ECGs, and ECOG performance status
- HRQoL using the additional parameters as measured by EORTC QLQ-C30, QLQ-OG25 plus GP and EQ5D-5L questionnaires
- Pharmacokinetics of zolbetuximab, C_{trough}
- Immunogenicity of zolbetuximab as measured by the frequency of anti-drug antibody (ADA) positive subjects.

Exploratory:

- TTP, defined as the time from the date of randomization until the date of PD as assessed by IRC per RECIST 1.1.
- Progression Free Survival 2 (PFS2), defined as the time from the date of randomization until the date of PD (per investigator) following subsequent anticancer therapy, death from any cause or start of any other anticancer therapy, whichever is earliest.
- DCR, defined as the proportion of subjects who have a BOR of stable disease (SD), CR or PR as assessed by IRC per RECIST 1.1.
- Potential genomic and/or other exploratory biomarkers that may be related to treatment outcome of zolbetuximab
- HRU

Statistical Methods:

Sample Size Justification:

One interim analysis and 1 final analysis are planned for OS, while only 1 analysis is planned for PFS as final. The OS interim analysis will occur at the same time of final PFS analysis (after pre-specified number of PFS events) and final OS analysis will be performed after the pre-specified

number of OS events are observed. The O'Brien-Fleming boundaries as implemented by Lan-DeMets (1983) alpha spending method (East®) will be used for the OS interim and OS final analyses. All statistical tests of treatment effects will be conducted at the 1-sided 0.025 level of significance unless otherwise specified.

Approximately 550 subjects will be randomized in a 1:1 ratio to receive zolbetuximab in combination with mFOLFOX6 chemotherapy (Arm A) or placebo in combination with mFOLFOX6 chemotherapy (Arm B).

The planned 300 PFS events during the study will provide 93.4% power to detect a difference in PFS between Arm A (zolbetuximab + mFOLFOX6) with the assumption of 9 months median PFS time and Arm B (placebo + mFOLFOX6) with the assumption of 6 months median PFS time (hazard ratio = 0.67) at the overall 1-sided 0.025 significance level. Similarly, the planned 396 OS events during the study will provide 81% power to detect a difference in OS between Arm A (zolbetuximab+mFOLFOX6) with the assumption of 14.7 months median survival time and Arm B (placebo + mFOLFOX6) with the assumption of 11 months median survival time (hazard ratio = 0.75) at the overall 1-sided 0.025 significance level.

Analysis Populations:

The full analysis set (FAS) will include all subjects who are randomized to 1 of the treatment arms. Subjects will be analyzed according to the treatment arm to which they were randomized. The FAS will be used for description of baseline characteristics and all efficacy analyses.

The safety analysis set (SAF) will contain all subjects who received at least 1 dose of any study drug (zolbetuximab/placebo/mFOLFOX6). The safety analysis set will be used for all safety analyses. Subjects would be analyzed according to the actual treatment they received.

The pharmacokinetic analysis set (PKAS) will consist of the subset of the SAF for which at least 1 zolbetuximab concentration measurement is available. Additional subjects may be excluded from the PKAS at the discretion of the Pharmacokineticist. The PKAS will be used for description of pharmacokinetic data.

Efficacy Analysis:

All efficacy analyses will be conducted using FAS.

Primary Efficacy Endpoint:

The primary efficacy endpoint of PFS will be analyzed using the stratified Log Rank Test with stratification factors to be specified in the SAP.

The hypothesis testing on the primary analysis will be performed at an overall 1-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in Arm A compared to Arm B versus the alternative hypothesis that PFS is prolonged in Arm A compared to Arm B.

Estimates of the treatment effect will be expressed as Hazard Ratio (HR) using a stratified Cox model, including 95% Confidence Interval (CI).

The sensitivity analysis for the primary efficacy endpoint will also be performed.

Secondary Endpoints:

The key secondary efficacy endpoint of OS will be analyzed using the stratified Log Rank Test with the same strata used in the analysis of PFS. To maintain the overall Type I error rate at the 0.025 significance level, the hypothesis testing on OS will be performed only if the null hypothesis on the primary analysis is rejected at the overall 1-sided 0.025 significance level. The key secondary TTCD endpoints of PF, OG25 Pain, and GHS/QoL will be analyzed using the same method as OS and PFS.

The secondary efficacy endpoint of ORR will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to control for the same strata used in the analysis of PFS and OS.

The secondary HRQoL endpoints collected via the EORTC QLQ-C30 and QLQ-OG25, GP and EQ-5D-5L will be analyzed with summary of change from baseline over time through the end of mFOLFOX6 treatment and inferential methods. Detailed analysis of HRQoL endpoints will be provided in the SAP.

Exploratory Endpoints: TTP and PFS2 will be analyzed in a similar way as PFS. However, in TTP analysis, deaths are not counted as events - rather, deaths are censored. DCR will be analyzed similarly as ORR. The HRU variables will be summarized by treatment arm.

Safety Analyses:

The safety evaluation will be based on AEs, clinical laboratory tests, vital signs, ECG and ECOG status. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment received.

All summaries of AEs will include only treatment-emergent events unless otherwise stated. AEs will be categorized by SOC and preferred term using MedDRA and will be graded for severity according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Pharmacokinetics:

Descriptive statistics (e.g., number of subjects, mean, standard deviation, minimum, median, maximum, coefficient of variation [CV], geometric mean, and geometric CV) will be provided for concentration of zolbetuximab. The potential relationship between zolbetuximab immunogenicity and zolbetuximab pharmacokinetics, efficacy, and safety profile may be assessed. Additional model-based analyses may be performed and reported separately.

Biomarkers:

Biomarkers will be summarized graphically or descriptively, and summary statistics may be tabulated. Associations between biomarkers and clinical (e.g., efficacy, safety or pharmacodynamics or pharmacokinetics) measures may be performed on subjects who have sufficient baseline and on-study treatment measurements to provide interpretable results for specific parameters.

Interim Analyses:

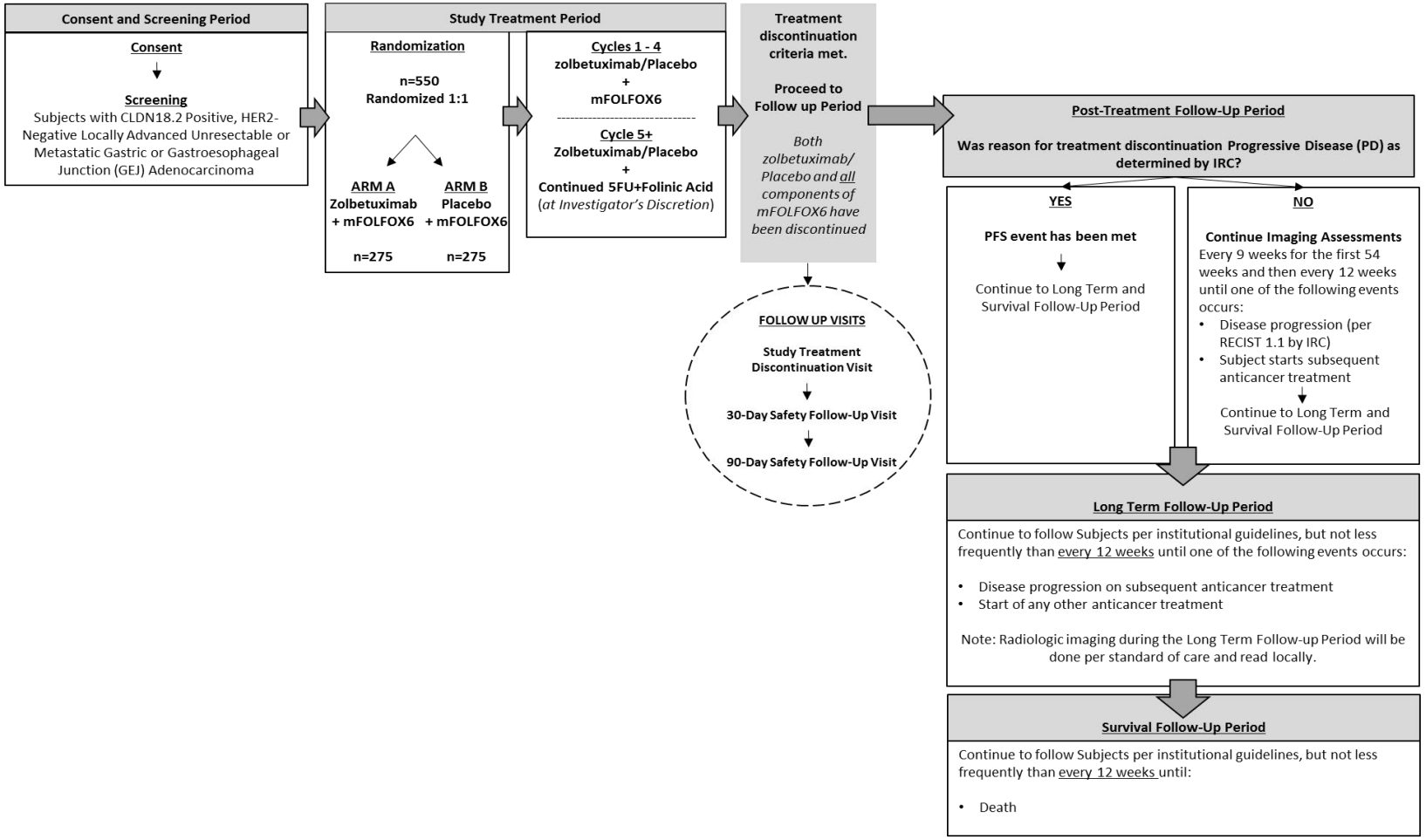
To evaluate whether zolbetuximab + mFOLFOX6 (Arm A) is particularly beneficial compared to placebo + mFOLFOX6 (Arm B) while the study is ongoing, a formal OS interim analysis is planned when the final PFS analysis occurs with the pre-specified number of PFS events. A group sequential design using the O'Brien-Fleming type alpha-spending function [Lan & DeMets, 1983] for efficacy will be utilized to control the overall 1-sided 0.025 significance level (East®) for the OS analyses.

The IDMC may recommend terminating the trial for favorable or unfavorable results at the formal efficacy interim analysis using PFS and OS. If the PFS is not significant at 0.025 1-sided alpha, the trial may be terminated for failure. In the case of favorable results, the 1-sided significance level for superiority is 0.0082, assuming about 72% of the target number of OS events is obtained, for the interim OS analysis and 0.0225 for the final OS analysis (Note: The OS significance boundary may be adjusted depending on the number of OS events at the time of interim analysis). If the 1-sided P value of the interim OS analysis is less than the significance level (and PFS is also significant at 1-sided 0.025 alpha), the IDMC may recommend terminating the trial for success. If the study is not stopped after the interim analysis, a final OS analysis will occur after 100% of the planned death events have been observed.

Details for the interim analyses, monitoring subject safety, enrollment rates and event (PFS/death) rates will be contained in the IDMC Charter. Recommendations regarding study conduct will be made by the IDMC based on their assessment of these rates.

V. FLOW CHART, STUDY SCHEMATICS, AND SCHEDULE OF ASSESSMENTS

a. Flow Chart



5-FU: fluorouracil; CLDN: Claudin; HER2: human epidermal growth factor receptor 2; IRC: independent review committee; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin; RECIST: Response Evaluation Criteria in Solid Tumors.

b. Study Treatment Period Dosing Schedule (1 Cycle = approximately 42 Days)

Cycles 1-4					Cycle 5+				
Day 1	Day 15	Day 22	Day 29	Days 30-42	Day 1	Day 15	Day 22	Day 29	Days 30-42
Z/P F	F	Z/P	F	No Treatment	Z/P 5-FU/FA	5-FU/FA	Z/P	5-FU/FA	No Treatment

Z/P = Zolbetuximab/Placebo

F = mFOLFOX6

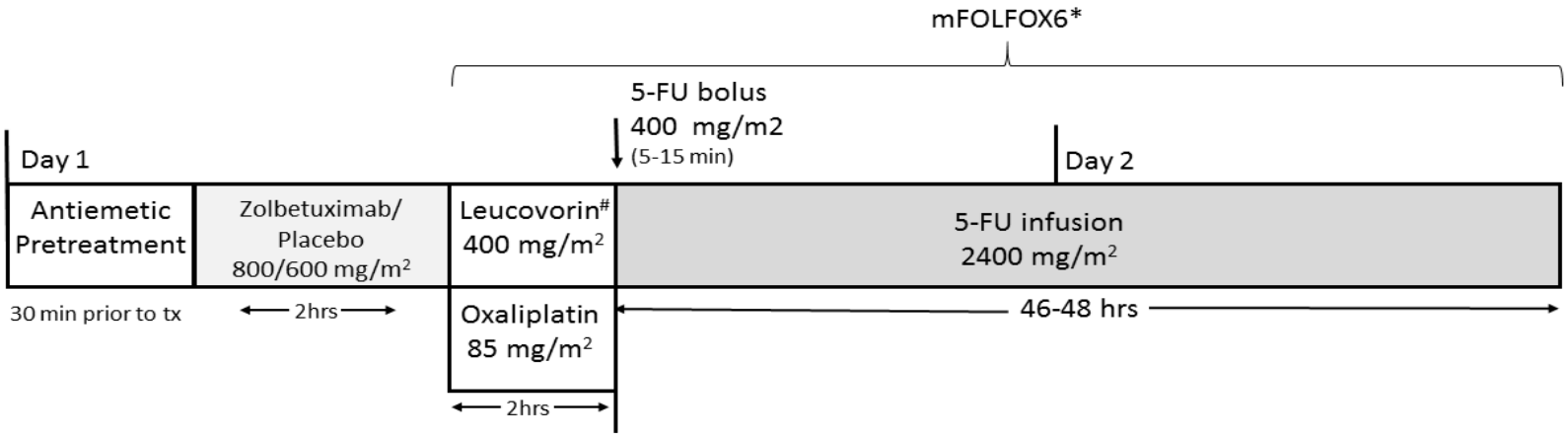
5-FU/FA = Continued 5-FU / Folinic Acid* (at discretion of Investigator)

* Or local equivalent

5-FU: fluorouracil

Dosing Schematics

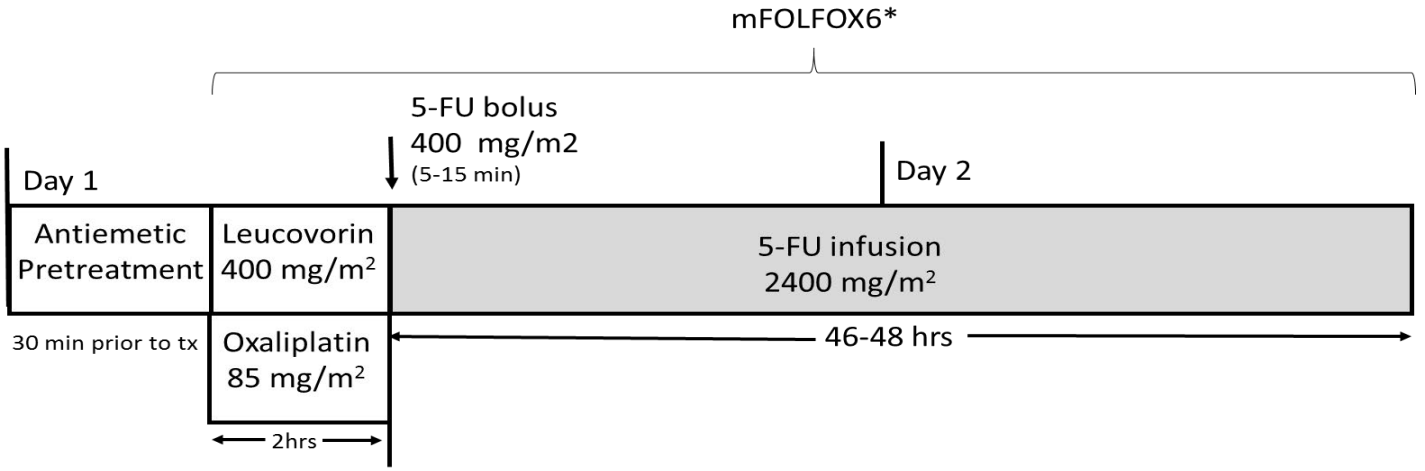
a. Combination Zolbetuximab/Placebo and mFOLFOX6 Dosing Visits (e.g., C1D1, C2D1, C3D1 and C4D1)



Note: Standard timeframes described above may be modified as per Section 5.1.2, Study Treatment Dose Modifications, Delays and Interruptions
*Cycles 5+: Subjects may continue on Leucovorin (or local equivalent) and 5-FU at Investigator's discretion
Or local equivalent

5-FU: fluorouracil; C1D1: Cycle 1 Day 1; C2D1: Cycle 2 Day 1; C3D1: Cycle 3 Day 1; C4D1: Cycle 4 Day 1; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin; tx: treatment

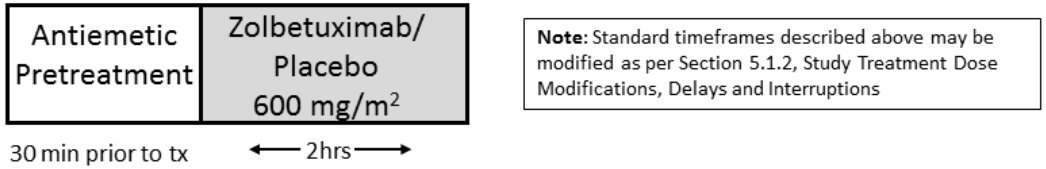
b. mFOLFOX6 Only Dosing Visits (e.g., C1D15, C1D29, C2D15, C2D29)



Note: Standard timeframes described above may be modified as per Section 5.1.2, Study Treatment Dose Modifications, Delays and Interruptions
*Cycles 5+: Subjects may continue on Leucovorin (or local equivalent) and 5-FU at Investigator's discretion

5-FU: fluorouracil; C1D15: Cycle 1 Day 15; C1D29: Cycle 1 Day 29; C2D15: Cycle 2 Day 15; C2D29: Cycle 2 Day 29; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin; tx: treatment

c. Zolbetuximab/Placebo Only Dosing Visits (e.g. C1D22, C2D22, C3D22, C4D22)



C1D22: Cycle 1 Day 22; C2D22: Cycle 2 Day 22; C3D22: Cycle 3 Day 22; C4D22: Cycle 4 Day 22; tx: treatment

Table 1 Schedule of Assessments

VISIT†	Screening [1]	Study Treatment Period (Each Cycle = approximately 42 Days)								Follow-up Period				
		Cycles 1 to 4 Zolbetuximab/Placebo + mFOLFOX6				Cycle 5+ Zolbetuximab/Placebo + 5FU + Folinic Acid (at investigator discretion)				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Day		1[5]	15	22	29	1	15	22	29					
Visit Window (calendar days)	-45 to -1	+ 6*	+ 6	+ 6	+ 6	+ 6	+ 6	+ 6	+ 6	+ 7	± 7	± 7	± 7	± 14
Informed Consent	X													
CLDN18.2 Tumor Sample[2]	X													
HER2 Tumor Sample[2]	X													
Biopsy (if applicable)[2]	X													
Medical and Disease History	X													
Confirmation of Inclusion/Exclusion Criteria[3]	X													
Randomization[3]		X												
Treatments														
Antiemetic Pretreatment[4]		X	X	X	X	X	X	X	X					
Zolbetuximab/Placebo[5]		X		X		X		X						
Post-Infusion Observation Period[6]		X		X		X		X						
mFOLFOX6[7,8]		X	X		X									
5FU + Folinic Acid[8]						X	X		X					
Safety Assessments														
Physical Examination[9]	X	X		X		X		X		X	X			
Weight[9]	X	X		X		X		X		X	X			
Vital Signs[10]	X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status[9]	X	X		X		X		X		X				
12-lead ECG[11]	X	X	X	If clinically indicated	X	If clinically indicated				X	X			
Image Assessment[12]	X[1]	Every 9 weeks ± 7 days from C1D1 for the first 54 weeks and then every 12 weeks ± 7 days thereafter												

Table continued on next page

VISIT†	Screening [1]	Study Treatment Period (Each Cycle = approximately 42 Days)								Follow-up Period				
		Cycles 1 to 4 Zolbetuximab/Placebo + mFOLFOX6				Cycle 5+ Zolbetuximab/Placebo + 5FU + Folinic Acid (at investigator discretion)				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Day		1[5]	15	22	29	1	15	22	29					
Visit Window (calendar days)	-45 to -1	+ 6*	+ 6	+ 6	+ 6	+ 6	+ 6	+ 6	+ 6	+ 7	± 7	± 7	± 7	± 14
Subject Contact[22]														X
Laboratory Tests														
Biochemistry[13]	X	X	X	X	X	X	X	X	X	X	X			
TSH and Free T4[13]	X	If clinically indicated								X				
Hematology[13]	X	X	X	X	X	X	X	X	X	X	X			
Coagulation Parameters (PT, PTT and INR)[14]	X	If clinically indicated												
DPD Deficiency Testing (per local requirements)	X													
Cytokine/Chemokine and/or Tryptase		If clinically indicated												
Urinalysis [13]	X	X		X		X		X		X	X			
Serum Pregnancy Test[15]	X	If clinically indicated and/or per local requirements												
Urine Pregnancy Test [16]		X		X		X		X		X	X			
Electronic Clinical Outcomes Assessments (eCOA)														
HRQoL[17]	X	X		X		X		X		X	X	X		
Health Resource Utilization (HRU) [17]		X		X		X		X		X	X	X		
Sampling														
Pharmacokinetic **zolbetuximab** [23]		X		X		X					X	X		
Anti-Drug Antibodies (ADA for Immunogenicity) [24]		X		X		X					X	X		
Genetic Immune Polymorphisms (Whole Blood)[25]		X												
Exploratory Biomarkers (Serum)[26]		X		X						X				
Exploratory Biomarkers (Plasma)[26]		X		X						X				
Whole Blood Sample for PGx (optional)[27]		X												
Post-Progression Tumor Sample (optional)[28]										X				
Concomitant Medication[29]	X	X	X	X	X	X	X	X	X	X	X	X		
AEs/SAEs[30]	X	X	X	X	X	X	X	X	X	X	X	X		

Footnotes appear on next page

AE: adverse event; βhCG: beta human chorionic gonadotropin; C1D1: Cycle 1 Day 1; CLDN: Claudin; CT: computerized tomography; ECG: electrocardiogram; eCOA: electronic Clinical Outcomes Assessment; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; FFPE: formalin fixed paraffin embedded; HER2: human epidermal growth factor receptor 2; HRQoL: health-related quality of life; HRU: Health Resource Utilization; ICF: informed consent form: INR: international normalized ratio; IRC: independent review committee; IRR: infusion-related reaction; IV: intravenous; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin; MRI: magnetic resonance imaging; OS: overall survival; PD: progressive disease; PFS: progression free survival; PFS2: progressive disease following 2nd line therapy; PGx: pharmacogenomics; PT: prothrombin time; PTT: partial thromboplastin time; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid stimulating hormone

†Local and/or regional protocols or precautions for COVID-19 management should be followed as applicable.

*+ 6 calendar day visit window does not apply to C1D1.

1. Screening: The Screening period is 45 days from full main ICF signature. Re-testing of lab values is allowed within the 45-day screening period. Re-screening outside of the 45-day window under a new subject number may be allowed once and upon discussion with the Medical Monitor. CT scans and MRIs conducted as part of a subject's routine clinical management (i.e., standard of care) obtained prior to signing the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the Screening period.
   - Optional Partial Screening: A partial screening ICF may be available for central testing of tissue for CLDN18.2 and HER2 only.
   - Laboratory testing:
     Eligibility can be determined based on central and/or local testing, however:
     - The most recent laboratory tests with available results must be used to confirm the subject's eligibility.
     - Central labs must be collected and submitted to the central laboratory during the Screening period.
     - If retesting of lab values is necessary to confirm eligibility, local labs can be used without requiring additional sample collection for central laboratory submission.
     - The screening labs used to determine eligibility should be collected within 14 days prior to randomization.
   - Radiologic imaging used to confirm eligibility must be conducted within 28 days prior to randomization.
2. CLDN18.2 and HER2 Testing: FFPE tumor tissue will be collected for central testing to determine CLDN18.2 and HER2 status. Archival tumor tissue from the primary tumor (gastric or GEJ) is preferred. If primary tumor tissue is not available, tumor tissue from a metastatic site (excluding bone metastasis) may be used. A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum of 15 FFPE unstained slides are required, as allowed per local policy. If slides are submitted, the slides should be freshly cut from the FFPE block within the time frame described in the laboratory manual. If local HER2 results are already available from local testing, a minimum of 12 FFPE unstained slides are required to be submitted to the central lab, as allowed per local policy. If the specimen is insufficient or unavailable, a biopsy may be performed to obtain primary tumor tissue (preferred) or tumor tissue from metastatic site (excluding bone metastasis). Sponsor pre-approval is required when the sole purpose of the biopsy procedure is to assess eligibility for this study. See [Section 5.7.3 Tumor Tissue Samples].

   If the required number of slides cannot be provided, the sponsor or designee should be contacted for further guidance.
3. Randomization: After confirmation of eligibility, the blinded site user will perform the randomization IRT transaction. The unblinded pharmacist/designee will be notified by the IRT system about the randomly assigned treatment. Confirmation of Inclusion/Exclusion Criteria must be completed prior to randomization. Randomization may be performed prior to C1D1. If C1D1 cannot be performed within 5 calendar days from Randomization, please contact the Medical Monitor. Details of infusion preparation and storage requirements are defined in the Pharmacy Manual and Infusion Guidelines.

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4. Antiemetic Pre-treatment: Antiemetic premedication (prophylactic antiemetics) should be administered prior to each study treatment. IV antiemetic premedication should be initiated prior to treatment, or oral antiemetic premedication should be initiated at a minimum of 30 minutes prior to treatment. Antiemetic premedication should be given according to institutional standard of care, published guidelines and the respective product package insert(s). For further details, see [Section 5.1.1.2 Antiemetics].
5. Zolbetuximab/placebo will be administered as a minimum 2-hour IV infusion every 3 weeks starting on C1D1 (i.e., C1D1, C1D22, C2D1, etc.). Please refer to the Pharmacy Manual and Infusion Guidelines for more detailed information. If both zolbetuximab/placebo and mFOLFOX6 are to be administered during the same visit, zolbetuximab/placebo should be administered prior to mFOLFOX6. For further details, see [Section 5.1.1.1 Zolbetuximab/Placebo].
6. Post-Infusion Observation Period: Following the first dose of zolbetuximab/placebo in C1, the subject must be observed for 2 hours post zolbetuximab/placebo infusion. The post-infusion observation period can be conducted during the mFOLFOX6 administration. If any ≥ grade 2 AEs are observed during infusion or during the post-infusion observation period, subsequent zolbetuximab/placebo infusion times should be extended and subjects should continue to be observed for 2 hours post zolbetuximab/placebo infusion. If the subject does not develop any ≥ grade 2 AEs, the subject should be observed for 1 hour post-infusion for their subsequent zolbetuximab/placebo infusions. The subject should be instructed to notify site personnel if they develop any AEs during this observation time period. In the event of an IRR with features of anaphylaxis (regardless of grade) or grade 3 or 4 IRR, blood, samples for cytokine/chemokine panel and serum total tryptase level (levels typically peak within 3 hours after the onset of symptoms) should be collected once the subject has stabilized for shipment to the central laboratory. See Observation Period following zolbetuximab/placebo [Section 5.4.2] for further details.
7. mFOLFOX6 will be administered every 2 weeks starting at C1D1 (i.e., C1D1, C1D15, C1D29, etc.) for 4 cycles (up to 12 treatments). A maximum of 12 doses of oxaliplatin can be administered. If both zolbetuximab/placebo and mFOLFOX6 are to be administered during the same visit, zolbetuximab/placebo should be administered prior to mFOLFOX6. See [Section 5.1.1.3 mFOLFOX6].
8. 5-FU and Folinic Acid may continue to be administered at the discretion of the investigator after completion of 12 treatments of mFOLFOX6. If 5-FU is not continued after 12 treatments of mFOLFOX6, then day 15 and day 29 visits are not required. If both zolbetuximab/placebo and 5-FU and folinic acid are to be administered during the same visit, zolbetuximab/placebo should be administered first. See [Section 5.1.1.1 Zolbetuximab/Placebo].
9. Physical Exam: should include height (at Screening only), weight and ECOG performance status. A full physical exam is required at Screening. The physical exam only needs to be repeated on C1D1 if clinically significant changes from Screening are observed (in the opinion of the investigator). For all cycles, the physical examination, weight and ECOG performance status assessments can be completed up to 48 hours prior to zolbetuximab/placebo administration. Targeted (symptom driven) physical exams should be conducted every 3 weeks on zolbetuximab/placebo visit days. For further details, see [Section 5.4.4 Physical Examination].
10. Vital signs (pulse, blood pressure, temperature) should be taken during every visit at the following time points (see [Section 5.4.1 Vital Signs]):
    - Pre-dose at every visit
    - C1D1: Every 30 (± 10) minutes during zolbetuximab/placebo infusion
    - If the subject did not develop any ≥ grade 2 AEs during the C1D1 zolbetuximab/placebo infusion or the Post-Infusion Observation Period, the site may do the following for subsequent zolbetuximab/placebo infusions:
        - The post-infusion observation period can be 1 hour for subsequent visits after C1D1
        - The vital signs can be assessed every 60 minutes for subsequent visits after C1D1
    - Every 60 (±10) minutes post zolbetuximab/placebo infusion during the Post-Infusion Observation Period (for 1 or 2 hours. See footnote 6)
    - Unscheduled if clinically indicated

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11. ECGs: ECGs will be locally read. When collected on the same day, ECG should be collected prior to pharmacokinetic samples. For further details, see [Section 5.4.5 Electrocardiogram]. A single ECG will be performed at the following time points:
    - Screening
    - Up to 48 hours prior to every oxaliplatin infusion (before any antiemetic treatment)
    - Up to 6 hours following completion of every oxaliplatin infusion
    - Zolbetuximab/placebo study treatment discontinuation visit
    - Zolbetuximab/placebo 30-day safety follow-up visit
    - If clinically indicated and/or per local requirements
12. Imaging Assessments: Radiologic imaging will be evaluated at Screening (must be conducted within 28 days prior to randomization) and every 9 weeks (± 7 days) counting from C1D1 for the first 54 weeks and then every 12 weeks (± 7 days) thereafter until subject develops radiological disease progression per RECIST 1.1 by IRC or starts other systemic anticancer treatment, whichever comes earlier. Imaging schedule should be maintained regardless of treatment delay. Imaging will include CT scans with contrast of the thorax, abdomen, and pelvis. If CT scan with contrast is medically not feasible, MRI may be used for imaging. Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease in bone or brain is suspected, respectively. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change. For randomized subjects, screening imaging should be sent to the central imaging vendor no later than submission of the first on-treatment imaging. All imaging acquired post randomization will be sent to the central imaging vendor within 7 days of scanning for the blinded independent central assessment of radiological tumor response based on RECIST 1.1. The investigator should make every effort to immediately submit radiologic assessments for IRC review when PD is suspected. See [Section 5.3 Efficacy Assessments]. Refer to Imaging Acquisition Guidelines for further detail on scan modality and contrast options.
13. Laboratory Assessments: See [Section 5.4.3 Laboratory Assessments] for list of laboratory assessments. Laboratory tests must be sent to the central laboratory for analysis unless otherwise approved by the sponsor. For screening/eligibility laboratory assessments, see footnote 1.
    - Laboratory test results (central or local) will be reviewed by the investigator prior to any study treatment. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.
    - Local laboratory results may be used for treatment decisions; however, central laboratory samples must also be drawn per protocol and sent to the central laboratory unless otherwise approved by the sponsor.
    - Central and local labs may be collected up to 48 hours prior to study treatment.
    - Holidays and weekends should be taken into account when scheduling these sample collections.
    - Additional assessments may be done centrally or locally to monitor AEs or as clinically indicated.
14. Coagulation (PT, PTT and INR): Coagulation tests should be done at Screening and during study treatment period if clinically indicated. Local or central lab results may be used to confirm eligibility. Ongoing evaluation should be continued for Subjects who are receiving therapeutic anticoagulation according to local standard of care. See [Section 5.4.3 Laboratory Assessments].
15. Serum Pregnancy Test: Serum pregnancy tests will be collected for female subjects of child bearing potential only. Serum pregnancy tests collected at Screening, during study treatment period and if clinically indicated or per local requirements. Serum pregnancy test can be completed up to 48 hours prior to zolbetuximab/placebo administration. (Note: For Screening, subjects with elevated serum βHCG and a demonstrated non-pregnant status through additional testing are eligible.) Local or central laboratory results may be used to confirm eligibility.

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16. Urine Pregnancy Test: for female subjects of child bearing potential only. Local urine pregnancy tests to be performed during the treatment period every 3 weeks at zolbetuximab/placebo visits and at the zolbetuximab/placebo Study Treatment Discontinuation and 30-Day Safety Follow up Visits. Urine pregnancy test can be completed up to 48 hours prior to zolbetuximab/placebo administration. Additional urine pregnancy testing for up to 9 months after the final study treatment administration may be applied based on local requirements.
17. HRQoL and HRU questionnaires: eCOA questionnaires are to be completed by the subject at Screening (except HRU), on day 1 and day 22 of each cycle (or up to 48 hours) before any antiemetic or drug treatment and before the disease status is discussed with the subject using the electronic tablet device provided. When completion by the subject is not possible, the questionnaires may be administered to the subject by site personnel using the electronic tablet device. For subjects with low literacy, situations where translations are unavailable or other circumstances preventing the screening questionnaires to be completed, please contact the sponsor for further guidance.
18. Study Treatment Discontinuation Visit (End of Study Treatment): The Study Treatment Discontinuation Visits will take place ≤ 7 days following the decision to discontinue all study treatment (zolbetuximab/placebo and mFOLFOX6 (all components). If zolbetuximab/placebo and mFOLFOX6 (all components) are discontinued on a different day, subjects will have a separate Study Treatment Discontinuation Visit following each treatment's discontinuation. Laboratory tests must be sent to the central laboratory for analysis. HRQoL and HRU questionnaires are not required at mFOLFOX6 treatment discontinuation visit. A combined visit can be completed if zolbetuximab/placebo are discontinued on the same day.
19. 30-Day Safety Follow-up Visit: A 30-Day Safety Follow-up visit should occur 30 days after the last dose of zolbetuximab/placebo and will include the assessments as shown in the Schedule of Assessments above. A 30-Day Safety Follow-Up Visit should occur 30 days after the last dose of mFOLFOX6 (all components) and may be conducted by phone if the subject is unable to visit the site and will require only contact for AE/SAE collection. HRQoL and HRU questionnaires are not required at mFOLFOX6 30-day safety follow up visit. A combined visit can be completed if zolbetuximab/placebo and all components of mFOLFOX6 are discontinued on the same day and HRQoL and HRU questionnaires should be completed for a combined visit.
20. 90-Day Safety Follow-up Visits: A 90-Day Safety Follow-up visit should occur 90 days after the last dose of zolbetuximab/placebo will include the assessments as shown in the Schedule of Assessments above. A 90-Day Safety Follow-Up Visit should occur 90 days after the last dose of mFOLFOX6 (all components) and may be conducted by phone if the subject is unable to visit the site and will require only contact for AE/SAE collection. HRQoL and HRU questionnaires are not required at mFOLFOX6 90-day safety follow up visit. A combined visit can be completed if zolbetuximab/placebo and all components of mFOLFOX6 are discontinued on the same day and HRQoL and HRU questionnaires should be completed for a combined visit.
21. Post-Treatment Follow-up: if a subject discontinues all study treatments (zolbetuximab/placebo and all components of mFOLFOX6) prior to IRC confirmed radiological disease progression, the subject will enter the Post-Treatment Follow-up Period and continue to undergo imaging assessments every 9 weeks (or every 12 weeks if subject has been on study over 54 weeks) until radiologic disease progression (i.e., PFS) or the subject starts subsequent anticancer treatment, whichever occurs earlier. If study treatment (zolbetuximab/placebo and all components of mFOLFOX6) is discontinued due to PD, the subject will enter the Long Term and Survival Follow-up Period.
22. Long Term and Survival Follow-up Period: Following disease progression on 1st line treatment or start of subsequent anticancer treatment, subjects will be followed in the Long-Term and Survival Follow-up Period per institutional guidelines, but at least every 12 weeks. Radiologic imaging will be done per standard of care and read locally. Survival Follow-up Period will continue until death (from any cause). All post-progression details including subsequent anticancer treatment and date and site of progression will be recorded on the eCRF. Subject contact by phone or other remote methods is sufficient during Long Team and Survival Follow-up.

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23. Pharmacokinetic (Serum) for zolbetuximab/placebo samples will be taken at the below timepoints and sent to the central laboratory. The date and time of each blood sample collection will be recorded to the nearest minute.
    - Cycle 1 Day 1: End of zolbetuximab/placebo infusion
    - Cycle 1 Day 22: Predose
    - Cycle 2 Day 1: End of zolbetuximab/placebo infusion
    - Pre-dose on Day 1 of Cycles 3, 5, 7 and 9
    - Zolbetuximab/placebo 30-Day Safety Follow-up visit
    - Zolbetuximab/placebo 90-Day Follow-up visit
    - Unscheduled pharmacokinetic blood samples may be taken at any time during the study to evaluate drug exposure following a safety event

    Pharmacokinetic Sampling Window:
    - Predose: within 60 minutes prior to dosing
    - End of Infusion: within 10 minutes after the end of the infusion
24. Anti-Drug Antibodies (ADA): Blood samples (Serum) for ADA will be taken at the below timepoints and sent to the central laboratory.
    - Cycle 1 Day 1: Predose
    - Cycle 1 Day 22: Predose
    - Pre-dose on Day 1 of Cycle 3, 5, 7 and 9
    - Zolbetuximab/placebo 30-Day Safety Follow-up visit
    - Zolbetuximab/placebo 90-Day Follow-up visit

    ADA Sampling Window: Predose: within 60 minutes prior to dosing
25. Genetic Immune Polymorphism: To be collected per local policy. Whole blood sample taken at C1D1 will be sent to the central laboratory. Samples may be collected up to 48 hours prior to study treatment.
26. Exploratory Biomarker (Serum and Plasma): To be collected per local policy. Samples should be taken at the below timepoints and sent to the central laboratory:
    - Cycle 1 Day 1: Predose
    - Cycle 1 Day 22: Predose
    - Cycle 2 Day 1: Predose
    - Cycle 2 Day 22: Predose
    - Cycle 3 Day 1: Predose
    - Cycle 3 Day 22: Predose
    - Cycle 4 Day 22: Predose
    - Zolbetuximab/placebo Study Treatment Discontinuation Visit

    Exploratory Biomarker samples may be collected up to 48 hours prior to study treatment
27. Optional PGx: for subjects who signed a separate ICF, an optional whole blood sample for PGx for exploratory biomarker analysis may be collected at up to 48 hours prior to first study drug administration at C1D1. Sample collection is optional and only collected as allowed per local policy.

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28. Optional Post-Progression Tumor Sample: for subjects who signed a separate ICF, an optional post-progression tumor sample for exploratory biomarker analysis may be collected following IRC confirmation of disease progression and prior to initiation of subsequent anticancer therapy. Sample collection is optional and only collected as allowed per local policy.
29. Concomitant medications: Concomitant medications will be collected from the time of full main informed consent through 90 days following the last dose of study treatment.
30. AEs/SAEs: AEs/SAEs (regardless of causality) will be collected from the time of full main informed consent through 90 days following the last dose of study treatment. See [Section 5.5.5 Reporting of Serious Adverse Events].

1 INTRODUCTION

Gastric and gastroesophageal junction (GEJ) cancers are among the malignancies with the highest unmet medical need. Gastric cancer-related mortality is the fourth leading cause of cancer death worldwide, even if its incidence has decreased over the last 50 years in different regions of the world [Cancer Fact Sheet, 2018; Amiri et al, 2011]. On the other hand, the incidence of subjects with GEJ adenocarcinoma has increased in recent decades, coinciding with a shift in histological type and primary tumor location [Waddell et al, 2013; Sahin et al, 2008].

In 2017, an estimated 723,100 people died worldwide from gastric cancer [Lederman 2017]. The overall 5-year survival rate for gastric and GEJ cancers is averaging 20% in the US and Europe, despite aggressive standard treatments, which are also associated with substantial side effects [Pennathur et al, 2013; Sahin et al, 2008].

There is no single standard, globally accepted first-line reference chemotherapeutic regimen for advanced gastric cancer. In the US and Europe, the current standard of care cytotoxic chemotherapy regimen consists of fluoropyrimidine with platinum-based combination chemotherapy regimens with or without a third agent such as docetaxel or epirubicin [National Comprehensive Cancer Network (NCCN), 2017; Waddell et al, 2013; Pasini et al, 2011]. Subjects in this study will receive mFOLFOX6 (a combination of fluorouracil [5-FU], folinic acid and oxaliplatin), which is a globally accepted standard-of-care treatment for subjects with locally advanced unresectable metastatic gastric or gastroesophageal (GE) cancer. The safety of this combination regimen is well-documented [Lee, HH et al, 2010].

The lack of a major benefit from the various newer generation combination chemotherapy regimens for these cancers has stimulated research into the use of targeted agents such as monoclonal antibodies (mAbs). Two mAbs, trastuzumab and ramucirumab, have received approval for treatment of gastric cancer. Trastuzumab selectively binds the extracellular domain of human epidermal growth factor receptor 2 (HER2), which is overexpressed in approximately 20% to 30% of gastric tumors [Bang et al, 2009], and ramucirumab specifically binds vascular endothelial growth factor (VEGF) receptor 2 and blocks binding of VEGF receptor ligands VEGF-A, VEGF-C and VEGF-D. Trastuzumab is approved for treatment of HER2 overexpressing metastatic gastric or GEJ adenocarcinoma while ramucirumab is approved as a single agent or in combination with paclitaxel, for treatment of advanced gastric or GEJ adenocarcinoma, with disease progression on or after prior fluoropyrimidine-or platinum-containing chemotherapy [CYRAMZA Prescribing Information, 2017; HERCEPTIN Prescribing Information, 2016]. These agents prolonged median overall survival (OS) by 4 or fewer months when given alone or in combination with chemotherapy compared with standard of care cytotoxic chemotherapy [Fuchs et al, 2014; Wilke et al, 2014; Ohtsu et al, 2011; Bang et al, 2010].

Approximately 70% to 80% of subjects with metastatic or advanced unresectable gastric and GEJ adenocarcinoma in the first line setting have tumors that are HER2 negative and are not treatable with trastuzumab. These subjects have an expected median survival of approximately 1 year. Therefore, a significant unmet medical need exists for the first-line

treatment of subjects with HER2 negative locally advanced or metastatic unresectable gastric and GEJ cancers. Zolbetuximab (IMAB362) is being developed with the goal of addressing this unmet medical need.

1.1 Background

Zolbetuximab is a genetically engineered, highly purified chimeric (mouse/human IgG1) antibody directed against the tight junction molecule Claudin 18.2 (CLDN18.2). The target is a member of the claudin family of more than 20 structurally related proteins that are involved in the formation of tight junctions in epithelia and endothelia [Niimi et al, 2001]. Tight junctions, together with adherens junctions and desmosomes, form the apical junctional complex in epithelial and endothelial cellular sheets. Adherens junctions and desmosomes are responsible for the mechanical adhesion between adjacent cells, whereas tight junctions are essential for the tight sealing of the cellular sheets forming a luminary barrier and controlling the paracellular ion flux.

CLDN18.2 is a 27.8 kDa protein with 4 membrane-spanning domains and 2 small extracellular loops [Gunzel & Yu, 2013; Sahin et al, 2008]. Zolbetuximab recognizes the first extracellular domain of CLDN18.2 with high affinity and specificity. Zolbetuximab does not bind to any other claudin family member including the closely related splice variant 1 of Claudin 18 (CLDN18.1).

CLDN18.2 is a highly cell type specific differentiation antigen that is expressed by differentiated gastric mucosa cells in the pit and base regions of gastric glands. Moreover, CLDN18.2 is not detectable in any other normal cell type of the human body either at transcript level or as protein. This highly selective tissue distribution pattern results in CLDN18.2 expression being strictly confined to a subpopulation of gastric epithelial cells in normal tissue [Sahin et al, 2008].

CLDN18.2 is expressed in a diversity of human cancers and is the dominant isoform in GE and pancreatic cancer [Lee et al, 2011]. The expression of CLDN18.2 is retained upon malignant transformation of gastric epithelia and is present in 81% of primary gastric adenocarcinomas. CLDN18.2 expression is frequently detected in diffuse and in intestinal gastric cancers. The CLDN18.2 protein is also localized in lymph node metastases of gastric cancer adenocarcinomas and in distant metastases into the bile duct, lung and especially into the ovary (so-called Krukenberg tumors). Furthermore, over 42% of esophageal adenocarcinomas and 50% to 70% of pancreatic cancers display significant expression of CLDN18.2 [Woll et al, 2014; Lee et al, 2011; Sanada et al, 2010; Karanjawala et al, 2008; Sahin et al, 2008].

Zolbetuximab is being developed for the first-line treatment of adult subjects with locally advanced unresectable or metastatic CLDN18.2-positive, HER2-negative gastric or GEJ adenocarcinoma in combination with platinum- and fluoropyrimidine-based chemotherapy. For this study, a subject's tumor must express CLDN18.2 in ≥ 75% of tumor cells demonstrating moderate to strong membranous staining as determined by central immunohistochemistry (IHC) testing.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical Data

In vitro studies with CLDN18.2-positive and negative cancer cell lines showed that zolbetuximab binds to the extracellular domain 1 of CLDN18.2 on human gastric cancer cell lines with high relative affinity and selectivity. In vitro assays demonstrated that zolbetuximab mediated an efficient lysis of CLDN18.2-positive cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

All zolbetuximab-mediated effects are strictly CLDN18.2 antigen-specific.

In bio-distribution studies in nude mice with human tumor xenografts, intravenously (IV) administered zolbetuximab was retained, as well as specifically and strongly enriched in CLDN18.2-positive human xenografts. No or little in vivo binding of zolbetuximab to any other mouse tissues including stomach tissue was observed.

Administration of repeated doses of zolbetuximab to mice bearing CLDN18.2-positive tumors resulted in retardation of tumor growth kinetics in tumor models.

A series of experiments were conducted with CLDN18.2-expressing cell lines derived from NUGC-4 and KATO-III to investigate the effects of combining these chemotherapy agents with zolbetuximab. Combinations of chemotherapy agents used in the treatment of gastric and esophageal cancers, including 5-FU, oxaliplatin and epirubicin (e.g., 5-FU/oxaliplatin, 5-FU/oxaliplatin/epirubicin) augmented zolbetuximab activity. In vitro pre-sensitization of human gastric cancer cells with chemotherapy resulted in an increase in the amount of cell surface CLDN18.2 and thus improved zolbetuximab-mediated ADCC and CDC.

In immunocompetent mice, zolbetuximab in combination with chemotherapy resulted in a pronounced T cell infiltration into the tumors and significant long-term survival benefit over zolbetuximab alone. Most likely this effect was mediated by induction of adaptive T cell immunity, which may have led to a prolonged antitumor effect and immune surveillance.

CLDN18.2 is highly conserved across species, and the epitope of zolbetuximab is identical between humans, mice and cynomolgus monkeys. In addition, the binding affinity of zolbetuximab to CLDN18.2 orthologs from mice, humans and cynomolgus monkeys was shown to be comparable, providing sufficient evidence that testing in mice and monkeys covers the potential on-target effects and toxicities of zolbetuximab.

The nonclinical pharmacology studies conducted with zolbetuximab provide sufficient experimental evidence that zolbetuximab depletes CLDN18.2-positive cells via ADCC and CDC. Cytotoxic drugs were shown to increase CLDN18.2 expression on human cancer cells and to improve the activity of the major mechanism of action (ADCC and CDC). Hence, the combination of zolbetuximab with first-line chemotherapy is being investigated in the clinic.

Safety pharmacology and toxicity of zolbetuximab were assessed in mice and cynomolgus monkeys. In mice, the maximum exposure tested was 300 mg/kg weekly over 13 weeks, and in cynomolgus monkeys, the maximum exposure tested was 100 mg/kg weekly over 4 weeks.

In both species, no target organs of toxicity were identified; however, in monkeys, emesis was observed in a non-dose-related manner. The emesis that was observed in monkeys was not severe and spontaneously resolved despite continued dosing. The emetic potential of zolbetuximab was confirmed in an investigational study in ferrets. This effect is considered to be related to the binding of zolbetuximab to junctional protein, CLDN18.2, in the gastric epithelium. A human tissue cross-reactivity study of zolbetuximab showed that the gastric mucosa was the only tissue with strong membrane staining. However, histological assessment of the gastric tissue in monkeys failed to identify any histopathological lesions.

Besides the findings listed previously, no other zolbetuximab-related adverse effects were observed in any organ, neither clinically, nor macroscopically or histologically upon postmortem analysis.

In summary, the nonclinical data outlined above supports the clinical development of zolbetuximab in combination with standard chemotherapy for the treatment of CLDN18.2-positive gastric or GEJ adenocarcinoma.

1.2.2 Clinical Data

Zolbetuximab has been evaluated in clinical studies as a single agent and in combination with epirubicin, oxaliplatin and capecitabine (EOX) chemotherapy or in combination with immunomodulation therapy (zoledronic acid [ZA] with or without interleukin-2 [IL-2]) for the treatment of adult subjects with CLDN18.2-positive advanced adenocarcinoma of the stomach, esophagus or GEJ.

CLDN18.2 expression was immunohistochemically determined for all subjects enrolled in the clinical studies. Several studies had an enrichment type of design meaning that only subjects above a certain threshold of CLDN18.2 positivity in their tumors were eligible for treatment. Eligibility for enrollment in the GM-IMAB-001-03 (EudraCT No. 2011-005285-38) and GM-IMAB-001-04 (EudraCT No. 2011-005509-64) studies, hereafter referred to as FAST and PILOT, respectively, was determined using the analytically validated and Conformité Européene-marked diagnostic kit, CLAUDETECT^{TM}18.2.

To date, 4 clinical studies have been completed and include GM-IMAB-001 (EudraCT No. 2008-004719-37, referred to as first-in-human [FIM]), PILOT, FAST and GM-IMAB-001-02 (EudraCT No. 2009-017365-36), referred to as MONO.

Zolbetuximab has been granted orphan drug designation for the treatment of stomach cancer by the EMA and FDA.

Clinical data from the studies described above supports the clinical development of zolbetuximab in combination with standard chemotherapy for the treatment of CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinomas.

1.3 Summary of Key Safety Information for Study Drugs

As of 06 May 2019, zolbetuximab has been administered to 306 subjects, including 259 subjects in the following 4 completed clinical studies:

- FIM study as a single monotherapy dose (up to 1000 mg/m^2) in 15 subjects;
- MONO study as repeated monotherapy doses up to 600 mg/m^2 once every 2 weeks in 54 subjects (maximum exposure was 72 infusions);
- FAST study as repeated doses of zolbetuximab in combination with EOX chemotherapy (up to 1000 mg/m^2 once every 3 weeks) in 162 subjects (maximum exposure greater than 40 infusions); and
- PILOT study in combination with immunomodulation therapy (up to 600 mg/m^2 once every 3 weeks) in 28 subjects.

And 2 ongoing open-label clinical studies:

- 8951-CL-0103 (ILUSTRO) as monotherapy or in combination with mFOLFOX6 in 32 subjects, and
- 8951-CL-0104 as monotherapy in 15 Japanese subjects.

Current phase 1/2 study status and enrollment are available in the zolbetuximab Investigator's Brochure (IB) (see end-of-text Table 4.1 in the IB).

Nausea and vomiting have been confirmed as important identified risks as has hypersensitivity reactions (HSRs), including infusion-related reactions (IRRs). Anemia and neutropenia are considered important potential risks. These important identified risks along with important potential risks, based on observations from the clinical studies, are described in Section 5.2 of the IB. Expected adverse drug reactions, including Reference Safety Information (RSI) used for expedited health authority reporting are described in Appendix 1 of the IB.

One patient from an ongoing phase 2 study (monotherapy arm) experienced grade 4 acute coronary syndrome, grade 4 cardiac arrest, grade 4 posterior reversible encephalopathy syndrome (PRES) and grade 3 pulmonary embolism, 22 days after the first infusion of zolbetuximab monotherapy. The patient had a medical history significant for uncontrolled hypertension, asthenia, and anemia. The patient recovered from these events that were deemed serious and a possible causal relationship to zolbetuximab could not be excluded. Refer to Section 6 of the IB for additional details.

In clinical studies, adverse reactions with nausea and/or vomiting and HSRs up to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 3 were reported. Subjects receiving zolbetuximab should receive prophylactic antiemetic medications, but do not need to be premedicated for prevention of HSRs and IRRs; however, subjects should be closely monitored for IRRs to facilitate early identification and management. In the case of zolbetuximab-induced nausea, vomiting or hypersensitivity including IRRs, the infusion rate of zolbetuximab may be reduced or the infusion may be paused or discontinued based on investigator's clinical judgement about severity of toxicity and local standard of care.

Detailed information on the toxicities associated with mFOLFOX6 can be found within Section 4.8 of the summary of product characteristics (SPC) for each component. Potential overlapping toxicities during treatment with zolbetuximab in combination with mFOLFOX6 include nausea, vomiting, abdominal pain, anemia and neutropenia.

1.4 Efficacy

1.4.1 Efficacy of Zolbetuximab

1.4.1.1 Efficacy Results from Study GM-IMAB-001-02 (MONO)

In the MONO study, efficacy analyses included subjects who received zolbetuximab at least once (Full Analysis Set [FAS]) at doses of 300 mg/m^2 (3 subjects) and 600 mg/m^2 (40 subjects). The best overall confirmed response for FAS subjects in the zolbetuximab 600 mg/m^2 dose group was partial response [PR] in 4 subjects (10.0%) that ranged in duration from 43 through 1037 days (GM-IMAB-001, Listing 13.2.6.4). The best overall confirmed response was stable disease (SD) in 6 subjects (15.0%) and progressive disease (PD) in 28 subjects (70.0%) in the 600 mg/m^2 group (GM-IMAB-001-02, Table 12.3.7.1). No subject achieved complete response (CR). Median progression free survival (PFS) in the FAS was 10 weeks (95% confidence interval [CI]: 8.6, 10.1 weeks) in the 600 mg/m^2 group (GM-IMAB-001-02, Table 12.3.3.1).

1.4.1.2 Efficacy Results from Study GM-IMAB-001-03 (FAST)

Treatment groups in the FAST study are referred to as EOX, EOX + IMAB600 (EOX plus zolbetuximab 600 mg/m^2 once every 3 weeks, with a loading dose of 800 mg/m^2 in Cycle 1) and EOX + IMAB1000 (EOX plus zolbetuximab 1000 mg/m^2 once every 3 weeks).

In the FAST study, efficacy analyses of all randomized subjects were included in the intent-to-treat set and included subjects randomized to EOX only (85 subjects), EOX + IMAB600 (79 subjects) and EOX + IMAB1000 (88 subjects). Additional analyses were completed for the FAS, defined as randomized subjects who received at least 1 dose of any study drug (E, Ox, capecitabine or zolbetuximab). The FAS differed from the intent-to-treat set (all randomized subjects) by 6 subjects all of whom discontinued the study early without death or post-baseline tumor assessment. The reasons for early discontinuation of these subjects included protocol violation (1 subject), physician decision (1 subject), withdrawal by subject (2 subjects) and AE (1 subject was anemic and another had a deep vein thrombosis) (GM-IMAB-001-03, Listing 13.2.1).

<u>PFS Based on Central Independent Review (Kaplan-Meier Model, Intent-to-Treat)</u>

The addition of zolbetuximab to EOX led to a statistically significant prolongation of PFS, both for the lower zolbetuximab dose (hazard ratio [HR] 0.45, $P < 0.0005$) and the higher zolbetuximab dose (HR 0.57, $P = 0.0114$). Median PFS was 7.5 months in the EOX + IMAB600 arm and 7.1 months in the EOX + IMAB1000 arm vs 5.3 months in the EOX arm, representing a median PFS prolongation by 2.2 and 1.8 months, respectively [IB, Table 17].

Overall Survival (Kaplan-Meier, Intent-to-Treat)

The addition of zolbetuximab 600 mg/m^2 led to a statistically significant prolongation in OS (HR 0.52, P < 0.0005). Median OS was 13 months in the EOX + IMAB600 arm vs 8.3 months in the EOX arm, representing an increase in median OS by 4.7 months. In the EOX + IMAB1000 arm, median OS was 9.6 months and hence, numerically longer than in the EOX arm [IB, Table 18]. However, the difference between the groups did not reach statistical significance. The difference in OS between the 2 zolbetuximab doses was statistically significant (P = 0.0406) (GM-IMAB-001-03, Table 12.3.2.1.5.3).

No major imbalances were seen between the treatment groups in the subsequent use of any anticancer therapy (EOX: 38.1%; EOX + IMAB600: 40.3%; EOX + IMAB1000: 34.1%) and any chemotherapy (EOX: 34.5%; EOX + IMAB600: 39.0%; EOX + IMAB1000: 29.4%) (GM-IMAB-001-03, Tables 12.2.1.1.5.1 and 12.2.1.5 [Safety-evaluable Set]).

Best Objective Tumor Response by Independent Review Committee

Based on confirmed responses, the ORR was 38.0% in the EOX + IMAB600 arm, 29.5% in the EOX + IMAB1000 arm and 24.7% in the EOX arm [IB, Table 21]. This included 10.1% of subjects with a CR in the EOX + IMAB600 arm, 4.5% in the EOX + IMAB1000 arm and 3.5% in the EOX arm (GM-IMAB-001-03, Table 12.3.3.1.3).

1.4.2 Efficacy of mFOLFOX6

Subjects in this study will receive mFOLFOX6 (a combination of fluorouracil [5-FU], folinic acid and oxaliplatin), which is an accepted standard-of-care treatment for subjects with locally advanced unresectable metastatic gastric or gastroesophageal (GE) cancer [NCCN 2017].

1.5 Risk Benefit Assessment

Zolbetuximab is an investigational agent for the treatment of CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma in combination with standard of care oxaliplatin fluoropyrimidine-based combination chemotherapy as first-line treatment.

Based on clinical efficacy and safety data from the MONO study, preliminary data from the FAST study and supportive preclinical pharmacological studies, there is potential of achieving clinically relevant benefit in combination with oxaliplatin and fluoropyrimidine-based chemotherapy in a first-line setting and as a single agent in the later line setting.

Based on currently available clinical data, zolbetuximab was tolerated from a safety perspective and most observed AEs have been considered manageable. Nonclinical toxicity data were supportive of clinical findings.

Important identified risks of zolbetuximab are:

- Nausea
- Vomiting
- HSRs (including IRRs)

Important potential risks of zolbetuximab include:

- Neutropenia
- Anemia

Management of the important identified risks associated with zolbetuximab includes antiemetic pretreatment reduction of the initial zolbetuximab infusion rate, and pausing or discontinuing the infusion based on patient tolerability and investigator's clinical judgment about severity of toxicity and local standard of care. Subjects receiving zolbetuximab do not need to be premedicated for prevention of HSRs and IRRs; however, subjects should be closely monitored for IRRs to facilitate early identification and management.

Overall, the risks, both identified and potential associated with zolbetuximab in combination with mFOLFOX6 are balanced by the anticipated benefits to subjects with CLDN18.2-positive, HER2 negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.

As described in [Section 10.1], an Independent Data Monitoring Committee (IDMC) will be responsible for reviewing the unblinded data from the trial to ensure the safety of the subjects.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Primary Objectives

The primary objective is to evaluate the efficacy of zolbetuximab plus mFOLFOX6 compared with placebo plus mFOLFOX6 (as first-line treatment) as measured by PFS in subjects with Claudin (CLDN)18.2 positive, HER2–negative locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma

2.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate efficacy as measured by Overall Survival (OS) as a key secondary objective
- To evaluate the physical function (PF), OG25-Pain and GHS/QoL scores as measured by European Organization for Research and Treatment of Cancer (EORTC) as a key secondary objective
- To evaluate efficacy as measured by Objective Response Rate (ORR)
- To evaluate efficacy as measured by Duration of Response (DOR)
- To evaluate safety and tolerability of zolbetuximab
- To further evaluate other health related quality of life (HRQoL) using additional parameters as measured by EORTC QLQ-C30, QLQ-OG25, Global Pain (GP) and the EuroQOL Five Dimensions Questionnaire 5L (EQ5D-5L) questionnaires
- To evaluate the pharmacokinetics of zolbetuximab
- To evaluate the immunogenicity profile of zolbetuximab

2.1.3 Exploratory Objectives

The exploratory objectives are:

- To evaluate efficacy as measured by Time to Progression (TTP)
- To evaluate PFS following second-line anticancer treatment (PFS2)
- To evaluate Disease Control Rate (DCR)
- To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome to zolbetuximab and mFOLFOX6.
- To evaluate Health Resource Utilization (HRU)

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This global, multi-center, double-blind, 1:1 randomized, phase 3 study will evaluate efficacy of zolbetuximab plus mFOLFOX6 versus placebo plus mFOLFOX6 as first-line treatment in subjects with CLDN18.2-positive, HER2-negative locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma.

PFS is the primary outcome. Secondary outcomes include OS, ORR, DOR, safety and tolerability, HRQoL, pharmacokinetic and the immunogenicity profile of zolbetuximab. Exploratory outcomes include TTP, PFS2, DCR biomarkers and HRU.

Approximately 550 subjects will be 1:1 randomized into 1 of 2 treatment arms:

- Arm A (mFOLFOX6 chemotherapy in combination with zolbetuximab)
- Arm B (mFOLFOX6 chemotherapy in combination with placebo)

Randomization of subjects will be stratified by the following factors:

- Region (Asia vs Non-Asia)
- Number of organs with metastatic sites (0 to 2 vs ≥ 3)
- Prior gastrectomy (Yes or No)

Screening

The Screening period is 45 days from full main informed consent form (ICF) signature. Retesting of lab values is allowed within the 45-day Screening period. Re-screening outside the 45-day window under a new subject number may be allowed once and upon discussion with the Medical Monitor. Computerized tomography (CT) scans and magnetic resonance imaging (MRI) conducted as part of a subject's routine clinical management (i.e., standard of care) obtained prior to signing the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the Screening period.

An optional partial screening ICF may be available to allow central testing of tissue for CLDN18.2 and HER2 only.

Formalin fixed paraffin embedded (FFPE) tumor tissue will be collected for central testing to determine CLDN18.2 and HER2 status.

- Archival tumor tissue is preferred.
    - A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum* of 15 FFPE unstained slides are required, as allowed per local policy. If slides are submitted, the slides should be freshly cut from the FFPE block within the time frame described in the laboratory manual.
    - If local HER2 results are already available from local testing, a minimum* of 12 FFPE unstained slides are required to be submitted to the central laboratory, as allowed per local policy.

      *If the required minimum number of slides is not able to be submitted, sponsor notification and approval is required.
- If the specimen is insufficient or unavailable, a biopsy may be performed to obtain tumor sample.
    - Sponsor pre-approval is required when the sole purpose of the biopsy procedure is to assess eligibility for this study.
    - If the required number of slides cannot be provided, the sponsor or designee should be contacted for further guidance.

Re-screening

Subjects who have failed screening are allowed to be re-screened one time after consultation with the Medical Monitor. Upon re-screening, a new subject number will be assigned. Subjects have to re-consent to the study and all screening procedures must be repeated, with the exception of the CLDN18.2 and HER2 testing, as well as the radiologic imaging procedure to confirm eligibility if the scan is within 28 days prior to randomization.

Laboratory values re-tested within the original 45-day Screening period are not considered re-screening and no new subject number will be assigned.

Treatment Period

Subjects will be treated with either zolbetuximab (Arm A) or placebo (Arm B) on Days 1 and 22 starting at C1D1 until the subject meets study treatment discontinuation criteria.

Subjects will also receive up to 12 treatments of mFOLFOX6 (or components of mFOLFOX6 if some components are discontinued due to toxicity) over 4 or more cycles (each cycle is approximately 42 days) in which mFOLFOX6 is administered on Days 1, 15 and 29 of each cycle. A maximum of 12 doses of oxaliplatin is permitted. After 12 mFOLFOX6 treatments, subjects may continue to receive 5-FU and folinic acid on Days 1, 15 and 29 of each cycle at the investigator's discretion until the subject meets study treatment discontinuation criteria.

(NOTE: An ECG is required to be performed and assessed locally prior to every oxaliplatin infusion [before any antiemetic treatment] and following completion of every oxaliplatin infusion. ECG should be performed up to 48 hours *prior* to and up to 6 hours *following* every oxaliplatin infusion. Oxaliplatin administration and electrolyte levels should be managed according to the investigator's judgment for subjects with grade 1 or 2 hypokalemia, hypomagnesemia and/or hypocalcemia.)

Study Treatment Discontinuation and Safety Follow-up Visits

Following discontinuation from zolbetuximab/placebo, subjects will have a zolbetuximab/placebo Study Treatment Discontinuation Visit, and 30- and 90-day Safety Follow-up Visits following their last dose of zolbetuximab/placebo.

Additionally, if mFOLFOX6 (all components) is discontinued on a different day than zolbetuximab/placebo, subjects will also have a Study Treatment Discontinuation Visit, and 30- and 90-day Safety Follow-up Visits following the last dose of mFOLFOX6 (all components). The mFOLFOX6 30- and 90-day Safety Follow-up Visits may be conducted by phone if the subject is unable to visit the site and will require only contact for AE/SAE collection.

Post-Treatment Follow-up Period (for PFS)

If a subject discontinues all study treatments (zolbetuximab/placebo and all components of mFOLFOX6) prior to IRC-confirmed radiological disease progression, the subject will enter the Post-Treatment Follow-up Period and continue to undergo scheduled imaging assessments every 9 weeks (or every 12 weeks if subjects has been on study over 54 weeks) until radiologic disease progression (i.e., PFS event) or the subject starts any other anticancer treatment (2nd line), whichever occurs earlier.

If study treatment (zolbetuximab/placebo and all components of mFOLFOX6) is discontinued due to disease progression (PFS event), the subject will enter the Long Term and Survival Follow-up Period.

Long Term Follow-up Period (for PFS2) and Survival Follow-up (for OS) Period

Following disease progression on first-line treatment or start of any other anticancer treatment, subjects will be followed in the Long-Term and Survival Follow-up Period per institutional guidelines, but not less frequently than every 12 weeks to confirm survival status (i.e., OS) and collect subsequent anticancer treatment details and progression status until PD following subsequent anticancer therapy (PFS2) is documented or the subject starts another systemic anticancer treatment, whichever occurs earlier. Radiologic imaging for PFS2 will be done per standard of care and read locally. The Survival Follow-up Period will continue until death (from any cause).

All post-progression details, including subsequent anticancer treatment and date and site of progression, will be recorded on the electronic case report form (eCRF). Subject contact by phone or other remote methods is sufficient during Long Team and Survival Follow-up. Additional follow-up contacts may be required per sponsor request for analysis purposes.
IDMC and Independent Data Analysis Center

Independent Data Monitoring Committee and Independent Data Analysis Center

An IDMC will be established and will monitor the benefit-risk of study treatment in an unblinded fashion per pre-defined IDMC charter. The first IDMC meeting will be approximately 6 weeks after the 40th subject enrolled has completed or discontinued Cycle 1 (6 weeks) and meetings will be conducted regularly thereafter, as determined by the IDMC.

An Independent Data Analysis Center will conduct an interim analysis of OS at the same time as the final PFS analysis, which will occur when approximately 300 PFS events have occurred. This analysis will be utilized by the IDMC to recommend whether the study should be stopped earlier than planned if zolbetuximab in combination with mFOLFOX6 has a favorable outcome compared with mFOLFOX6 in combination with placebo. If the OS interim analysis demonstrates a highly more favorable outcome for zolbetuximab in combination with mFOLFOX6, the study may be stopped for success. However, any subject continuing to derive clinical benefit from zolbetuximab/placebo in combination with mFOLFOX6 as assessed by the investigator will be allowed to continue treatment. The full procedures for IDMC review will be described in a separate IDMC charter.

2.2.2 Dose Rationale

The dose of zolbetuximab in this study is an 800 mg/m^2 loading dose (C1D1) followed by 600 mg/m^2 every 3 weeks in combination with mFOLFOX6. This dose and schedule of zolbetuximab (800/600 mg/m^2 every 3 weeks) were chosen based on the observed data from the GM-IMAB-001-03 (FAST) study. In the GM-IMAB-001-03 (FAST) study, addition of zolbetuximab 800/600 mg/m^2 every 3 weeks to EOX (Arm 2) demonstrated a statistically significant and clinically meaningful improvement on PFS and OS in subjects with CLDN18.2-positive advanced gastric/GEJ cancer compared to EOX (Arm 1). The mean serum trough concentration of zolbetuximab was maintained above the targeted value of 50 μg/mL (based on half maximal effective concentration [EC_{50}] of in vitro ADCC and CDC activities) following 800/600 mg/m^2 every 3 weeks administration. A higher zolbetuximab dose (1000 mg/m^2 every 3 weeks) in combination with EOX was added 18 months later (with the allocation ratio of 1:1:7) as Arm 3 in the FAST study to evaluate safety and efficacy at the higher dose. However, this arm had less treatment benefit compared to Arm 2. Although there were numerical differences observed in some demographics and baseline characteristics, the sample size was not sufficient to evaluate and confirm the impact of such differences; therefore, the reason for underperformance in Arm 3 remains inconclusive.

There is no single standard, globally accepted first-line reference chemotherapeutic regimen for advanced gastric cancer. A fluoropyrimidine (5-FU or capecitabine) in combination with platinum agent (cisplatin or oxaliplatin) is an accepted standard of care cytotoxic chemotherapy regimen in both Western and Asian countries [NCCN, 2017; Ajani et al, 2010; Ohtsu et al, 2011; Ajani, 2000; Kim et al, 1993]. Both classes of agents are considered to be interchangeable according to NCCN and European Society for Medical Oncology treatment guidelines. Subjects in this study will receive mFOLFOX6 (a combination of 5-FU, folinic acid and oxaliplatin), which is a globally accepted standard-of-care treatment for subjects with locally advanced unresectable metastatic gastric or GEJ cancer. The safety of this combination regimen is well-documented.

2.3 Endpoints

2.3.1 Primary Endpoints

The primary endpoint is PFS, which is defined as the time from the date of randomization until the date of radiological PD (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 by independent review committee [IRC]) or death from any cause, whichever is earliest.

2.3.2 Secondary Endpoints

The secondary endpoints are:

- OS, defined as the time from the date of randomization until the date of death from any cause
- Time to confirmed deterioration (TTCD) using the PF, OG25-Pain and GHS/QoL scores as measured by EORTC QLQ-C30 and QLQ-OG25. TTCD is defined as time to first confirmed deterioration, i.e., time from randomization to first clinically meaningful deterioration that is confirmed at the next scheduled visit
- ORR, defined as the proportion of subjects who have a best overall response (BOR) of CR or PR as assessed by IRC per RECIST 1.1
- DOR, defined as the time from the date of the first response (CR/PR) until the date of PD as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest
- Safety and tolerability, as measured by AEs, laboratory test results, vital signs, ECGs and Eastern Cooperative Oncology Group (ECOG) performance status
- HRQoL using the additional parameters as measured by EORTC QLQ-C30, QLQ-OG25, GP and EQ5D-5L questionnaires
- Pharmacokinetics of zolbetuximab, C_{trough}
- Immunogenicity of zolbetuximab as measured by the frequency of anti-drug antibody (ADA) positive subjects.

2.3.3 Exploratory Endpoints

The exploratory endpoints are:

- TTP, defined as the time from the date of randomization until the date of PD as assessed by IRC per RECIST 1.1.
- PFS2, defined as the time from the date of randomization until the date of PD (per investigator) following subsequent anticancer therapy, death from any cause or start of any other anticancer therapy, whichever is earliest.
- DCR, defined as the proportion of subjects who have a BOR of SD, CR or PR as assessed by IRC per RECIST 1.1.
- Potential genomic and/or other exploratory biomarkers that may be related to treatment outcome of zolbetuximab
- HRU

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumors are CLDN18.2 positive, HER2-negative and who have not been previously treated for metastatic disease with chemotherapy (1st line).

For the purpose of this study, CLDN18.2-positive is defined as CLDN18.2 expression in ≥ 75% of tumor cells demonstrating moderate to strong membranous staining as determined by central IHC testing.

3.2 Inclusion Criteria

Waivers to the inclusion criteria will **NOT** be allowed.

General Criteria:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) must be obtained from the subject or legally authorized representative (if applicable) prior to any study-related procedures.
2. Subject is considered an adult (e.g., ≥ 18 years of age in the US) according to local regulation at the time of signing the informed consent.
3. Subject agrees not to participate in another interventional study while on study treatment.
4. A female subject is eligible to participate if she is not pregnant (negative serum pregnancy test at Screening; female subjects with elevated serum beta human chorionic gonadotropin (βhCG) and a demonstrated non-pregnant status through additional testing are eligible) and at least 1 of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 12.3 Contraception Requirements
    OR
    b. WOCBP who agrees to follow the contraceptive guidance as defined in Appendix 12.3 Contraception Requirements throughout the treatment period and for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs.
5. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 6 months after the final study treatment administration.
6. Female subject must not donate ova starting at Screening and throughout the study period, and for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs.
7. A sexually active male subject with female partner(s) who are of childbearing potential must agree to use contraception as detailed in Appendix 12.3 Contraception Requirements during the treatment period and for at least 6 months after the final study drug administration.

8. Male subject must not donate sperm starting at Screening and throughout the study period and for 6 months after the final study drug administration.
9. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or for the time partner is breastfeeding throughout the study period and for 6 months after the final study drug administration.

Disease Specific Criteria:

10. Subject has histologically confirmed diagnosis of Gastric or GEJ adenocarcinoma.
11. Subject has radiologically confirmed locally advanced unresectable or metastatic disease within 28 days prior to randomization.
12. Subject has radiologically evaluable disease (measurable and/or non-measurable disease according to RECIST 1.1), per local assessment, ≤ 28 days prior to randomization. For subjects with only 1 evaluable lesion and prior radiotherapy ≤ 3 months before randomization, the lesion must either be outside the field of prior radiotherapy or have documented progression following radiation therapy.
13. Subject's tumor expresses CLDN18.2 in ≥ 75% of tumor cells demonstrating moderate to strong membranous staining as determined by central IHC testing.
14. Subject has a known HER2-Negative tumor as determined by local or central testing on a gastric or GEJ tumor specimen.

Physical or Laboratory Findings

15. Subject has ECOG performance status 0 to 1.
16. Subject has predicted life expectancy ≥ 12 weeks in the opinion of the investigator.
17. Subject must meet all of the following criteria based on the centrally or locally analyzed laboratory tests collected within 14 days prior to randomization. In the case of multiple sample collections within this period, the most recent sample collection with available results should be used to determine eligibility.
    a. Hemoglobin (Hgb) ≥ 9 g/dL. Subjects requiring transfusions are eligible if post-transfusion hemoglobin ≥ 9 g/dL.
    b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    c. Platelets ≥ 100 x 10^9/L
    d. Albumin ≥ 2.5 g/dL
    e. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) without liver metastases (or < 3.0 x ULN if liver metastases are present)
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN without liver metastases (or ≤ 5 x ULN if liver metastases are present)
    g. Estimated creatinine clearance ≥ 30 mL/min
    h. Prothrombin time (PT)/international normalized ratio (INR) and PTT ≤ 1.5 x ULN (except for subjects receiving anticoagulation therapy)

3.3 Exclusion Criteria

Waivers to the exclusion criteria will **NOT** be allowed.

Subject who meets any of the following exclusion criteria prior to enrollment is not eligible for enrollment:

Prohibited Treatment or Therapies

1. Subject has received prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. However, subject may have received either neo-adjuvant or adjuvant chemotherapy, immunotherapy or other systemic anticancer therapies as long as it was completed at least 6 months prior to randomization. Subject may have received treatment with herbal medications that have known antitumor activity > 28 days prior to randomization.
2. Subject has received radiotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma ≤ 14 days prior to randomization and has not recovered from any related toxicity.
3. Subject has received systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to randomization. Subjects using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone), receiving a single dose of systemic corticosteroids or receiving systemic corticosteroids as premedication for radiologic imaging contrast use are allowed.
4. Subject has received other investigational agents or devices within 28 days prior to randomization.

Medical History or Concurrent Disease

5. Subject has prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanized or chimeric antibodies.
6. Subject has known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment.
7. Subject has prior severe allergic reaction or intolerance to any component of mFOLFOX6.
8. Subject has known dihydropyrimidine dehydrogenase (DPD) deficiency. (NOTE: Screening for DPD deficiency should be conducted per local requirements.)
9. Subject has a complete gastric outlet syndrome or a partial gastric outlet syndrome with persistent/recurrent vomiting.
10. Per investigator judgment, subject has significant gastric bleeding and/or untreated gastric ulcers that would exclude the subject from participation per investigator judgment.
11. Subject has a known history of a positive test for human immunodeficiency virus (HIV) infection or known active hepatitis B (positive HBs Ag) or C infection. NOTE: Screening for these infections should be conducted per local requirements.

a. For subjects who are negative for HBs Ag, but HBc Ab positive, an HB DNA test will be performed and if positive the subject will be excluded.
b. Subjects with positive hepatitis C virus (HCV) serology, but negative HCV RNA test results are eligible.
c. Subjects treated for HCV with undectable viral load results are eligible.

12. Subject has an active autoimmune disease that has required systemic treatment within the past 3 months prior to randomization.
13. Subject has active infection requiring systemic therapy that has not completely resolved within 7 days prior to randomization.
14. Subject has significant cardiovascular disease, including any of the following:
    a. Congestive heart failure (defined as New York Heart Association Class III or IV), myocardial infarction, unstable angina, coronary angioplasty, stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis within 6 months prior to randomization.
    b. History of clinically significant ventricular arrhythmias (i.e., sustained ventricular tachycardia, ventricular fibrillation or Torsades de Pointes)
    c. QTc interval > 450 msec for male subjects; QTc interval > 470 msec for female subjects
    d. History or family history of congenital long QT syndrome
    e. Cardiac arrhythmias requiring anti-arrhythmic medications (Subject with rate controlled atrial fibrillation for > 1 month prior to randomization are eligible).
15. Subject has history of central nervous system metastases and/or carcinomatous meningitis from gastric/GEJ cancer.
16. Subject has known peripheral sensory neuropathy > grade 1 unless the absence of deep tendon reflexes is the sole neurological abnormality.
17. Subject has had a major surgical procedure ≤ 28 days prior to randomization.
    a. Subject is without complete recovery from a major surgical procedure ≤ 14 days prior to randomization.
18. Subject has psychiatric illness or social situations that would preclude study compliance, per investigator judgment.
19. Subject has another malignancy for which treatment is required per investigator's clinical judgment.
20. Subject has any concurrent disease, infection or comorbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.

4 IDENTIFICATION OF STUDY TREATMENT(S)

4.1 Zolbetuximab (IMAB362) (Investigational Product)

The investigational product, zolbetuximab, is a sterile lyophilized powder with the chimeric (mouse/human IgG1) monoclonal antibody zolbetuximab as the active pharmaceutical ingredient.

The investigational product is supplied by Astellas in single-use glass vials containing 105 mg of zolbetuximab. All excipients are animal component free and of compendial grade (Pharm. Eur. current version). No preservatives are contained, since the vial is designed for single use.

The investigational product should be stored at refrigerated conditions (2°C to 8°C; 36°F to 46°F). Temperature should be controlled and monitored. Details of investigational product receipt, labeling, storage and preparation are provided in the Pharmacy Manual and Infusion Guidelines.

The zolbetuximab used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Global Development, Inc. (APGD), Astellas US Technologies, Inc. or sponsor's designee in accordance with APGD or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practices (GMP) guidelines, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each vial and carton will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

As required, a qualified person of Astellas Pharma Europe B.V. (APEBV) or sponsor's designee will perform the final release of the medication according to the requirements of the EU Directive 2003/94/EC annex 13.

4.2 0.9% Sodium Chloride Injection

0.9% Sodium Chloride Injection will be used for infusion solution preparation in this study for both zolbetuximab arm and placebo arm. 0.9% Sodium Chloride Injection will not be manufactured or provided to sites by the sponsor. Sites should use their own commercially obtained supply of 0.9% Sodium Chloride Injection. Details of preparation of infusion solution are provided in the Pharmacy Manual and Infusion Guidelines. ***SPECIFIC TO JAPAN:*** In this study, 0.9% Sodium Chloride Injection is not considered an 'investigational product' as defined in J-GCP.

For manufacturing, formulation, storage, handling and preparation details please refer to the package insert, SPC or local product information supplied by the manufacturer.

4.3 Comparative Drug (Placebo)

Placebo will not be manufactured or provided by the sponsor. Sites should use their own commercial supply of 0.9% Sodium Chloride Injection, as placebo infusion solution. Details of preparation of placebo infusion solution are provided in the Pharmacy Manual and Infusion Guidelines.

4.4 mFOLFOX6 (Backbone Treatment)

Oxaliplatin, folinic acid (leucovorin) and 5-FU (mFOLFOX6) are administered in combination with zolbetuximab/placebo. If folinic acid is not available it may be replaced by levo-folinic acid. mFOLFOX6 products should be given according to institutional standards,

published guidelines, the respective product package insert(s) or dosed according to this protocol. ***SPECIFIC TO JAPAN:*** leucovorin (folinic acid) is replaced by levofolinate.

Backbone treatment will be supplied by the responsible site pharmacy of each investigational site or by the sponsor as applicable. Sites are permitted to utilize generic drug that is approved by the respective regulatory authority.

For manufacturing, formulation, storage, handling and preparation details please refer to the package insert, SPC or local product information supplied by the manufacturer.

mFOLFOX6 will be supplied by the responsible site pharmacy of each investigational site or by the sponsor, as applicable.

If mFOLFOX6 is supplied by the sponsor, mFOLFOX6 used in this study will be, packaged and labeled under the responsibility of qualified staff at APGD/Astellas US Technologies, Inc. (AUST) sponsor's designee in accordance with APGD-AUST or sponsor's designee SOPs, GMP guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each product will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

As required, a qualified person of APEBV or sponsor's designee will perform the final release of the medication according to the requirements of the EU Directive 2003/94/EC annex 13.

4.5 Other Drug(s)

4.5.1 Antiemetic Premedication

Prophylactic antiemetics will not be provided by the sponsor but rather will be sourced by the Sites via commercial supply.

For manufacturing, formulation, storage, handling and preparation details please refer to the package insert, SPC or local product information supplies by the manufacturer.

4.6 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study treatment and other drug deliveries from the sponsor are received by the investigator or designee and that:

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- Any unused study drug is returned to the sponsor, unless prior approval is received from the sponsor allowing local standard procedures for the alternative disposition of unused study drug.

Study drug inventory and accountability records will be kept by the investigator, head of study site (***SPECIFIC TO SITES IN JAPAN***) or designee. Study drug accountability

throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site staff must return unused study drug to the sponsor or designee at the end of the study or upon expiration unless otherwise approved by the sponsor.

4.7 Blinding

4.7.1 Blinding Method

The clinical study will be conducted as subject and investigator-blinded. Subjects will be randomized to receive zolbetuximab or placebo in a blinded fashion such that neither the investigator, sponsor's study management team, clinical staff, nor subject will know which agent is being administered.

Upon the need for unblinding (e.g., real-time assessment of the safety data), the chair of the IDMC can ask for the release of the treatment assignment for 1 or more subjects and will identify the sponsor staff who will receive the information.

4.7.2 Confirmation of the Indistinguishability of the Study Drugs

The appearance and the final form of both the drug and packaging of zolbetuximab solution for infusion are identical to placebo. In order to maintain the blind, the subjects randomized to the placebo treatment arm (Arm B) will receive placebo in a volume and route corresponding to the appropriate zolbetuximab dose (Arm A). The unblinded pharmacist/designee will provide the investigator or designee with blinded study drugs to dose the subjects. Refer to the Pharmacy Manual and Infusion Guidelines for detailed information.

4.7.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study drug blind will be maintained by the Interactive Response Technology (IRT) system.

4.7.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The IRT will be programmed with blind-breaking instructions that may only be requested by the investigator or sub-investigators designated to have access to perform blind-break. No subjects or other study personnel, other than the unblinded pharmacist or designee, will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure. In case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment for the subject. Any unblinding by the investigators must be reported immediately to the sponsor and must include an explanation for the unblinding.

The investigator must have confirmed functionality to access code-break through the IRT system and must have a designated back up (e.g., redundant processes) to support emergency unblinding requirements.

Prior to randomization, subjects should be provided with information that includes the site emergency contact number and back-up contact number in case of a medical emergency. Any unblinding by the investigational staff must be reported immediately to the sponsor and include an explanation of why the study drug was unblinded. If unblinding is associated with a SAE the investigator is to follow the instructions in [Section 5.5.5 Reporting of SAE].

Care should be taken to limit knowledge of the randomization arm in case this could affect the blinding of other subjects or future study assessment for the subject.

The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file.

If possible, the sponsor should be contacted prior to unblinding of the study drug.

4.7.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

4.8 Assignment and Allocation

Subject randomization will be performed by blinded site user via IRT and treatment assigned in a 1:1 ratio to zolbetuximab or placebo. Prior to the initiation of the study treatment, the unblinded pharmacist/designee will be notified by the IRT system about the randomly assigned treatment. The unblinded pharmacist/designee will dispense the treatment according

to the IRT system's assignment. Specific procedures for randomization through the IRT are contained in the IRT manual.

Randomization will be stratified by:

- Region (Asia vs Non-Asia)
- Number of organs with metastatic sites (0 to 2 vs ≥ 3)
- Prior gastrectomy (Yes or No)

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 Zolbetuximab/Placebo

Subjects will be administered zolbetuximab/placebo as a minimum 2-hour IV infusion. **Guidance for slowing the initial infusion to minimize toxicity can be found in the Pharmacy Manual and Infusion Guidelines.** Subjects will be administered a loading dose of 800 mg/m^2 on zolbetuximab/placebo on C1D1 followed by subsequent doses of 600 mg/m^2 every 3 weeks starting from C1D22 (i.e., C1D22, C2D1, C2D22, etc.). If both zolbetuximab/placebo and mFOLFOX6 are to be administered during the same visit, zolbetuximab/placebo should be administered prior to mFOLFOX6. Flow rate data will be collected in the eCRF.

IV infusion may be interrupted or slowed down to manage toxicity. Please refer to the Pharmacy Manual and Infusion Guidelines for more detailed information.

5.1.1.2 Antiemetics

Antiemetic premedication (prophylactic antiemetics) should be administered prior to each study treatment.

(NOTE: Subjects receiving zolbetuximab do not need to be premedicated for prevention of IRRs; however, subjects should be closely monitored for IRRs to facilitate early identification and management.)

- Antiemetic premedication
  - IV antiemetic premedication should be initiated prior to treatment, or
  - Oral antiemetic premedication should be initiated at a minimum of 30 minutes prior to treatment.
- On days when zolbetuximab/placebo and mFOLFOX6 are administered together, antiemetic premedication should be given prior to zolbetuximab/placebo administration.
- It is recommended that the prophylactic antiemetic regimen include (but is not limited to) the following agents:
  - NK-1 receptor blockers
  - 5-HT3 receptor blockers*

* To minimize the risk of Torsades de Pointes, administer 5-HT3 receptor blockers with caution to subjects who have or may develop QTc prolongation.

Antiemetic premedication should be administered according to institutional standard of care, published guidelines and the respective product package insert(s).

Corticosteroids:

- The impact of corticosteroids on the potential efficacy of zolbetuximab is not known. Therefore, consideration should be given to avoid or minimize the use of corticosteroids as a prophylactic antiemetic, if possible.
- For a subject's first dose of zolbetuximab/placebo, it is recommended that the prophylactic use of corticosteroids be avoided.

5.1.1.3 mFOLFOX6

Subjects will receive up to 12 treatments of mFOLFOX6 (or components of mFOLFOX6 if some components are discontinued due to toxicity) over 4 or more cycles (each cycle is approximately 42 days) in which mFOLFOX6 is administered on Days 1, 15 and 29.

After 12 treatments, subjects may continue to receive 5-FU and folinic acid at the investigator's discretion until the subject meets study treatment discontinuation criteria.

mFOLFOX6 (or components) should be administered after zolbetuximab/placebo on visits when both treatments are to be administered on the same day (e.g., C1D1, C2D1, etc.).

- Oxaliplatin: 85 mg/m^2 IV infusion over 2 hours or longer per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle), for a maximum of 12 doses. (NOTE: ECG is required to be performed and assessed locally prior to every oxaliplatin infusion [before any antiemetic treatment] and following completion of every oxaliplatin infusion. ECG should be performed up to 48 hours prior to and up to 6 hours following every oxaliplatin infusion. Oxaliplatin administration and electrolyte levels should be managed according to the investigator's judgement for subjects with grade 1 or 2 hypokalemia, hypomagnesemia and/or hypocalcemia.)
- Folinic Acid: 400 mg/m^2 IV infusion over 2 hours or longer per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle). Folinic acid can be continued beyond 4 cycles based on investigator's judgement. SPECIFIC TO JAPAN: Or, Levofolinate 200 mg/m^2 IV infusion over 2 hours or longer per institutional standard of care every 2 weeks for 4 cycles. Levofolinate can be continued beyond 4 cycles based on investigator's judgement. Or, levo-folinic acid may be given as deemed appropriate by the investigator in accordance with institutional standard of care.
- 5-FU Bolus: 400 mg/m^2 IV bolus over 5 to 15 minutes or per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle). 5-FU can be continued beyond 4 cycles based on investigator's judgement.
- 5-FU Infusion: 2400 mg/m^2 IV infusion over 46 to 48 hours or per institutional standard of care every 2 weeks for 4 cycles (3 treatments each cycle). 5-FU can be continued beyond 4 cycles based on investigator's judgement.

5.1.2 Study Treatment Dose Modifications, Delays And Interruptions

5.1.2.1 Increase or Reduction of Zolbetuximab/Placebo

Dose increase or dose reduction for zolbetuximab/placebo is not allowed. Body surface area should be recalculated at minimum if there is a weight change of at least 10% since the last dose calculation.

5.1.2.2 Zolbetuximab/Placebo Interruption or Permanent Discontinuation

There is a + 6 calendar day allowable window for dosing zolbetuximab/placebo. If zolbetuximab/placebo treatment is delayed 7 or more calendar days then it should be administered with the next scheduled mFOLFOX6 treatment, which would now be considered Day 1 of the next cycle. The timing of subsequent doses should be scheduled using the date of the last dose administration. Refer to the Pharmacy Manual and Infusion Guidelines for further detail on incomplete dosing.

A delay of zolbetuximab/placebo treatment for > 28 days from when the next study treatment was scheduled (> 49 days from last dose of zolbetuximab/placebo) to be administered due to unresolved toxicity associated with zolbetuximab/placebo will result in the subject discontinuing zolbetuximab/placebo.

Radiologic imaging schedule of every 9 weeks (± 7 days) counting from C1D1 for the first 54 weeks, and then every 12 weeks (± 7 days) thereafter, should be maintained regardless of treatment delay.

Note: IV infusion of zolbetuximab/placebo should be administered as a minimum 2-hour infusion. IV infusion may be interrupted or slowed down to manage toxicity. Please refer to the Pharmacy Manual and Infusion Guidelines for more detailed information.

Guidelines for zolbetuximab/placebo treatment modification due to non-hematologic and hematologic toxicities, regardless of investigator assessment of relationship to zolbetuximab/placebo, are described below in Table 2 and Table 3, respectively.

One case of PRES has been reported in subjects receiving zolbetuximab. **Discontinue zolbetuximab/placebo if PRES is suspected.** Confirm PRES diagnosis by brain imaging, preferably by MRI.

Table 2 Guidelines for Zolbetuximab/Placebo Treatment Modification Due to Non-Hematologic Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Infusion-related reaction (IRR) *Other than nausea, vomiting, or abdominal pain* See Table 4 for further IRR management guidance	Continue Infusion	Interrupt infusion. Infusion may be resumed at a reduced rate when toxicity has improved to grade ≤ 1.	Stop the infusion immediately. Institute appropriate medical management immediately based on the type of reaction. Permanently Discontinue zolbetuximab/placebo	
Nausea	Continue Infusion		Interrupt infusion. Hold zolbetuximab/ placebo treatment until toxicity has improved to grade ≤ 1, then restart the infusion at a lower rate. If the investigator determines that the toxicity is not related to zolbetuximab and the toxicity has improved to grade ≤ 2, then infusion may be restarted at the investigator's discretion at a lower rate.	Not applicable*
Vomiting	Continue Infusion	Continue infusion unless treatment was held due to grade 3 or higher vomiting in which case treatment must be held until vomiting has improved to ≤ grade 1.	Interrupt infusion. Hold zolbetuximab/placebo treatment until toxicity has improved to grade ≤ 1 and then restart infusion at a lower rate.	Permanently Discontinue zolbetuximab/placebo
Other Non-Hematologic toxicity	Continue Infusion		Interrupt infusion. Hold zolbetuximab/placebo treatment until toxicity has improved to grade ≤ 1. If the investigator determines that the toxicity is not related to zolbetuximab and the toxicity has improved to grade ≤ 2, then infusion may be restarted at the investigator's discretion.#	Permanently Discontinue zolbetuximab/placebo
PRES	Discontinue zolbetuximab/placebo if PRES is suspected.			

PRES: posterior reversible encephalopathy syndrome.
*Grade 4 nausea is not defined in Common Terminology Criteria For Adverse Events v4.03. If investigator assesses nausea as grade 4, manage per local standard of care.
For subjects with a pulmonary embolism, treatment can continue without resolving to grade 2 or less.

Table 3 Guidelines for Zolbetuximab/Placebo Treatment Modification Due to Hematologic Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia†	ANC < LLN to 1500/mm^3; < LLN to 1.5 x 10^9/L	ANC < 1500 to 1000/mm^3; < 1.5 to 1.0 x 10^9/L	ANC < 1000 to 500/mm^3; < 1.0 to 0.5 x 10^9/L	ANC < 500/mm^3; < 0.5 x 10^9/L
Action	Continue treatment	Continue treatment unless treatment was held due to grade 3 or higher neutropenia in which case treatment must be held until ANC improves to ≤ grade 1.	Hold treatment and recheck blood counts weekly until ANC resolves to ≥ 1.5 x 10^9/L (≤ grade 1) before restarting treatment. Discontinue zolbetuximab/placebo if ANC remains < 1.5 x 10^9/L (≥ grade 2) after a ≥ 28-day treatment delay from when the next study treatment was scheduled to be administered.	
Febrile Neutropenia†	Not Applicable		Grade 3 ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.	Grade 4 Life-threatening consequences; urgent intervention indicated
Action			Follow standard/local management guidelines. Hold treatment and recheck blood counts weekly until ANC recovers to ≥ 1.5 x 10^9/L (grade ≤ 1) and fever has resolved. Discontinue zolbetuximab/placebo if ANC remains < 1.5 x 10^9/L (≥ grade 2) after a ≥ 28-day treatment delay from when the next study treatment was scheduled to be administered.	
Thrombocytopenia	PLT < LLN to 75,000/mm^3; < LLN to 75.0 x 10^9/L	PLT < 75,000 to 50,000/mm^3; < 75.0 to 50.0 x 10^9/L	PLT < 50,000 to 25,000/mm^3; < 50.0 to 25.0 x 10^9/L	PLT < 25,000/mm^3; < 25.0 x 10^9/L
Action	Continue treatment	Continue treatment unless treatment was held due to grade 3 or higher thrombocytopenia in which case treatment must be held until thrombocytopenia improves to ≤ grade 1.	Withhold treatment and recheck blood counts weekly until platelets recover to > 75× 10^9/L (grade ≤ 1) before restarting treatment. Discontinue zolbetuximab/placebo if PLT remains < 75 x 10^9/L (grade ≥ 2) after a ≥ 28-day treatment delay from when the next study treatment was scheduled to be administered.	
Anemia†	Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 to 80g/L	Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated

Table continued on next page

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Action	Continue treatment		Withhold treatment. Follow standard treatment guidelines. Transfuse if indicated. Recheck blood counts weekly until Hgb recovers to > 8.0 g/dL (≤ grade 2) before restarting treatment. Discontinue zolbetuximab/ placebo if Hgb remains < 8.0 g/dL (≥ grade 3) after a ≥ 28-day treatment delay from when the next study treatment was scheduled to be administered.	Withhold treatment. Urgent intervention required following standard treatment guidelines and transfuse blood. The subject may be discontinued after discussion with Medical Monitor.

ANC: absolute neutrophil count; PLT: platelet count; Hgb: hemoglobin

† At the investigator's discretion growth factors may be used according to standard practice guidelines.

5.1.2.3 Guidelines for Infusion-Related Reactions for Zolbetuximab/Placebo

Subjects should be closely monitored for IRRs to facilitate early identification and management.

The management of such toxicities should be based on investigator utilizing institutional standard of care, published guidelines, and the general guidelines provided in Table 4 below.

A subject with an infusion reaction should be evaluated specifically for the symptoms and signs that are highly suggestive of anaphylaxis (urticaria, repetitive cough, wheeze and throat tightness/change in voice). A careful examination of the skin is advised in order to detect urticaria, which often appears first in the neck, trunk, abdomen and axillae.

Not all anaphylactic reactions manifest as anaphylactic shock. Because anaphylaxis can recur and worsen with re-exposure, permanently discontinue zolbetuximab/placebo for any subject having a reaction with features (even if mild) that are highly suggestive of anaphylaxis.

Note: IV infusion of zolbetuximab/placebo should be administered as a minimum 2-hour infusion. IV infusion may be interrupted or slowed down to manage toxicity. Please refer to Pharmacy Manual and Infusion Guidelines for more detailed information.

Table 4 Infusion-Related Reactions

Infusion-Related Reactions	
Refer to Table 2 for management of IRRs of nausea, vomiting or abdominal pain.	
CTCAE v4.03 Grade	**Management**
Grade 1 standard infusion *reactions other than nausea, vomiting or abdominal pain#*	Continue infusion and closely monitor the subject.
Grade 2 standard infusion reaction *other than nausea, vomiting and abdominal pain #*	Interrupt. Medical management as per type of reaction. Resume infusion once toxicity grade ≤ 1 and reduce the infusion rate for the remaining infusion. For the next infusion: • Increase total infusion time (reduce infusion rate). • Pre-medicate as appropriate.* • Closely monitor the subject for symptoms and signs of an infusion reaction.
Any infusion reaction with features of anaphylaxis **OR** Grade 3 or 4 standard infusion reactions *other than nausea, vomiting and abdominal pain #*	Stop the infusion immediately. Institute appropriate medical management immediately based on the type of reaction. Permanently Discontinue zolbetuximab/placebo *Once the subject has been stabilized, collect blood for a cytokine/chemokine panel and serum total tryptase level (levels typically peak within 3 hours after the onset of symptoms) and send to the central laboratory.*

CTCAE v4.03: Common Terminology Criteria For Adverse Events version 4.03; IRR: infusion-related reaction

* At the investigator's discretion, anti-histamines may be used as premedication for the next infusion. Systemic corticosteroids should be avoided or minimized while subject is on study treatment unless required for management of an emergent medical condition (e.g., severe nausea/vomiting or hypersensitivity reaction).

For grade 3 or 4 IRR of nausea, vomiting or abdominal pain, collect blood for cytokine/chemokine panel and serum total tryptase level and send to the central laboratory.

5.1.2.4 mFOLFOX6 Dose Modification

There is a + 6 calendar day allowable window for mFOLFOX6 dosing. If treatment is delayed 7 or more calendar days then mFOLFOX6 should be administered at the next scheduled zolbetuximab/placebo treatment visit, which would now be considered day 1 of the next cycle. The timing of subsequent doses should be scheduled using the previous dosing visit date, irrespective of which treatment was administered.

Dosing and dose modification should be based on investigator utilizing institutional standard of care, approved package insert, SPC or local product information supplied by the manufacturer for each agent (oxaliplatin, folinic acid, 5-FU) and general guidelines provided below.

The first infusion of mFOLFOX6 should not be modified. After the assessment of tolerability, dose adjustments should be performed based on the investigator's judgement utilizing institutional standard of care, approved package insert, SPC or local product information and/or the recommended criteria in Table 5 based on maximum hematologic or non-hematologic toxicity data from the previous cycle as shown in Table 6 and Table 7,

respectively. Dose reduction criteria for oxaliplatin-related neurotoxicity are presented in Table 8. Each drug may be dose reduced independently based on the specific types of toxicities observed. It is recommended that no more than 2 dose reductions per drug per subject occur (see Table 5). Dose re-escalation is not recommended after treatment-related AEs. Dose re-escalation of 5-FU is permitted after the subject has completed 4 cycles or 12 doses of mFOLFOX6 and/or has permanently discontinued oxaliplatin if the investigator chooses to continue 5-FU. If further dose reduction is required beyond the criteria in Table 5, that component of mFOLFOX6 should be discontinued.

In subjects experiencing toxicity requiring a delay or discontinuation of mFOLFOX6, subject may continue to receive zolbetuximab/placebo as clinically appropriate. If mFOLFOX6 is withheld, subject should be evaluated weekly (at a minimum) until the toxicity has improved sufficiently at which time treatment can be restarted as described in the tables below (as applicable). A delay of study treatment for > 28 days from when the next study treatment was scheduled to be administered due to unresolved toxicity associated with mFOLFOX6 (> 42 days from the last dose of mFOLFOX6) will result in the subject discontinuing mFOLFOX6 (all components).

Prior to each 5-FU dose, subjects should receive folinic acid (400 mg/m^2 [or such dose deemed appropriate by the investigator]), or if unavailable, levofolinic acid/levofolinate (***SPECIFIC TO JAPAN***) (200 mg/m^2 [or such dose deemed appropriate by the investigator]). If both folinic acid and levofolinic acid are unavailable, they may be omitted from the treatment regimen. Folinic or levofolinic acid should be delayed if 5-FU treatment is delayed.

Table 5 Recommended Dose Adjustment Levels for Oxaliplatin and 5-FU

Drug		**Oxaliplatin**	**5-FU Bolus**	**5-FU Infusion**
Initial Dose		85 mg/m^2	400 mg/m^2	2400 mg/m^2
Dose Reduction	**Level 1**	65 mg/m^2	320 mg/m^2	1900 mg/m^2
	Level 2	50 mg/m^2	260 mg/m^2	1500 mg/m^2

5-FU: fluorouracil

If a subject has 5-FU discontinued or interrupted, oxaliplatin should be discontinued or interrupted until 5-FU is resumed. For additional information, refer to the approved package insert, SPC or local product information supplied by the manufacturer for each agent (oxaliplatin, folinic acid, 5-FU).

5.1.2.5 mFOLFOX6: Dose Modifications for Hematologic Toxicity

The mFOLFOX6 dose modifications for hematologic toxicity are presented in Table 6. Dose modifications should be maintained until recovery from hematologic toxicity. A delay of mFOLFOX6 for ≥ 28 days from when the next mFOLFOX6 was scheduled to be administered due to hematologic toxicity associated with mFOLFOX6 will result in the subject discontinuing mFOLFOX6 (all components).

Dosing and dose modification should be based on investigator utilizing institutional standard of care, approved package insert, SPC or local product information supplied by the manufacturer for each agent (oxaliplatin, 5-FU) and general guidelines provided below.

Table 6 mFOLFOX6 Dose Modification Due to Hematologic Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia†	ANC < LLN to 1500/mm^3; < LLN to 1.5 x 10^9/L	ANC < 1500 to 1000/mm^3; < 1.5 to 1.0 x 10^9/L	ANC < 1000 to 500/mm^3; < 1.0 –to 0.5 x 10^9/L	ANC < 500/mm^3; < 0.5 x 10^9/L
Action	Continue treatment.		Hold treatment and recheck blood counts weekly* until ANC resolves to ≥ 1.5 x 10^9/L before restarting treatment. Discontinue mFOLFOX6 if ANC remains < 1.5 x 10^9/L after a ≥ 28-day treatment delay.	
Dose Modification (for next treatment)	Maintain dose level.		Reduce oxaliplatin by 1 level.† If oxaliplatin is held, omit 5-FU bolus.	First event: Omit 5-FU bolus and reduce oxaliplatin by 1 level.† Second event: Reduce 5-FU infusion and oxaliplatin 1 dose level.†
Febrile Neutropenia†			ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.	Life-threatening consequences; urgent intervention indicated
Action			Follow standard treatment guidelines	Proceed to next treatment when fever has resolved and ANC recovers to ≥ 1.5 x 10^9/L within 28 days from when the next study treatment was scheduled to be administered.
Dose Modification (for next treatment)			First event: Omit 5-FU bolus and reduce oxaliplatin by 1 level.† Second event: Reduce 5-FU infusion and oxaliplatin 1 dose level.†	

Table continued on next page

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	PLT < LLN to 75,000/mm^3; < LLN to 75.0 x 10^9/L	PLT < 75,000 to 50,000/mm^3; < 75.0 to 50.0 x 10^9/L	PLT < 50,000 to 25,000/mm^3; < 50.0 to 25.0 x 10^9/L	PLT < 25,000/mm^3; < 25.0 x 10^9/L
Action	Continue treatment.		Withhold treatment and recheck blood counts weekly* until platelets recover to > 75× 10^9/L before restarting treatment. Discontinue mFOLFOX6 if PLT remains < 75 x 10^9/L after a ≥ 28-day delay from when the next study treatment was scheduled to be administered.	
Dose Modification (for next treatment)	Maintain dose level.		Reduce oxaliplatin 1 dose level. Omit bolus 5-FU if the subject is not receiving oxaliplatin.	First event: Omit 5-FU bolus and reduce oxaliplatin by 1 level.† Second event: Reduce 5-FU infusion and oxaliplatin 1 dose level.†

5-FU: fluorouracil; ANC: absolute neutrophil count; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin; PLT: platelet count

† At the investigator's discretion growth factors may be used according to standard practice guidelines.

* Weekly recheck with ± 3 day window for thrombocytopenia

5.1.2.6 mFOLFOX6: Dose Modification for Non-hematologic Toxicity

mFOLFOX6 dose modifications for non-hematologic toxicity should be based on the most severe toxicity experienced during the last treatment (Table 7). Retreatment should be delayed until recovery of all non-hematologic toxicity to ≤ grade 2 with the exception of increased bilirubin or ALT, which must recover to grade 1 or baseline, whichever was higher. The maximum permitted treatment delay is 28 days from when the next mFOLFOX6 treatment was scheduled to be administered (> 42 days from the last dose of mFOLFOX6) for recovery of non-hematologic toxicity. If the subject has not recovered sufficiently to meet retreatment criteria within that timeframe, mFOLFOX6 should be discontinued.

ECG is required to be performed and assessed locally prior to every oxaliplatin infusion (before any antiemetic treatment) and following completion of every oxaliplatin infusion. ECG should be performed up to 48 hours *prior* to and up to 6 hours *following* every oxaliplatin infusion. Oxaliplatin may be administered in the setting of grade 1 or grade 2 hypokalemia, hypomagnesemia and/or hypocalcemia, based on the investigator's judgement.

During or following study treatment, additional ECG monitoring should be initiated per local standard of care for subjects who experience syncope, presyncope, palpitations and/or bradycardia.

- If the QTc interval is > 450 msec, medically manage per local standard of care, including correction of hypokalemia, hypomagnesemia, and/or hypocalcemia.

- If the QTc interval is > 500 msec, medically manage per local standard of care, withhold oxaliplatin and 5-FU treatment, ensure continuous ECG monitoring, and obtain cardiology consultation. If the QTc interval resolves to ≤ 450 msec, the subject may resume treatment at 1 reduced dose level.

Dosing and dose modification should be based on investigator utilizing institutional standard of care, approved package insert, SPC or local product information supplied by the manufacturer for each agent (oxaliplatin, 5-FU) and general guidelines provided below.

Table 7 mFOLFOX6 Dose Modification Due to Non-hematologic Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea				
Action	Continue treatment	Start medical management for diarrhea. Continue treatment.	Start medical management for diarrhea. Withhold all mFOLFOX6 treatment. Restart treatment after diarrhea recovers to ≤ grade 2	
Dose Modification (for next treatment)	None	Maintain dose level. If grade 2 diarrhea persists despite medical management, reduce 5-FU bolus and 5-FU infusion 1 dose level.	Reduce 5-FU bolus and 5-FU infusion 1 dose level.	Reduce 5-FU bolus, 5-FU infusion and oxaliplatin 1 dose level
Other Non-hematologic Toxicities†‡				
Action			Withhold all mFOLFOX6 treatment until toxicity improves to ≤ grade 2.	
Dose Modification (for next treatment)			Reduce dose of drug(s) responsible for toxicity by 1 dose level. At the investigator's discretion, the 5-FU bolus may be omitted in lieu of or in conjunction with dose reduction(s) in the 5-FU infusion and/or oxaliplatin.	

5-FU: fluorouracil; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin

† For mucositis/stomatitis, decrease only 5-FU, not oxaliplatin.

‡ Exceptions: alopecia, fatigue, anorexia, nausea/vomiting (if can be controlled by antiemetics) and constipation (if can be controlled with laxatives, stool softeners, etc.).

5.1.2.7 Guidelines for Infusion-Related Reactions for mFOLFOX6

Subjects should be closely monitored for IRRs to facilitate early identification and management. The management of such toxicities should be based on investigator utilizing institutional standard of care.

5.1.2.8 Oxaliplatin-Induced Neurotoxicity

Oxaliplatin is known to be associated with peripheral neuropathy, including paresthesia and dysesthesia of the hands, feet and perioral region. Subjects treated with oxaliplatin in this study should be advised to avoid cold drinks and exposure to cold water or air, especially within 3 to 5 days of receiving oxaliplatin. Dose modifications for oxaliplatin related to neurotoxicity are presented in Table 8.

Cases of PRES have been reported in subjects receiving Oxaliplatin combination chemotherapy. Discontinue Oxaliplatin if PRES is suspected. Confirm PRES diagnosis by brain imaging, preferably MRI.

Table 8 Oxaliplatin Dose Modification for Associated Neurotoxicity

<table>
<tr><th>Toxicity/Duration</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>Paresthesia or dysesthesia</td><td>Paresthesia or dysesthesia‡ that does not interfere with function</td><td>Paresthesia or dysesthesia‡, interfering with function, but not activities of daily living</td><td>Paresthesia or dysesthesia‡ with pain or with functional impairment that also interferes with activities of daily living</td><td>Persistent paresthesia or dysesthesia that is disabling or life-threatening</td></tr>
<tr><td>1 to 7 Days</td><td rowspan="3">No dose reduction</td><td rowspan="2">No dose reduction</td><td><u>First Event:</u>
Reduce oxaliplatin by 1 dose level at next treatment.
<u>Second Event:</u>
Reduce oxaliplatin by a second dose level at next treatment.</td><td rowspan="3">Discontinue oxaliplatin</td></tr>
<tr><td>> 7 Days</td><td>For Grade 3 neurotoxicity > 7 days/persistent between treatments, discuss oxaliplatin discontinuation with Medical Monitor.</td></tr>
<tr><td>Persistent between treatments†</td><td>Reduce oxaliplatin by 1 dose level at next treatment</td><td>For Grade 3 neurotoxicity > 7 days/persistent between treatments, discuss oxaliplatin discontinuation with Medical Monitor</td></tr>
<tr><td>Acute laryngopharyngeal dysesthesia‡
(during or after the 2-hour infusion)</td><td colspan="4">Discontinue current infusion.
At next treatment, consider pretreatment with benzodiazepines and increasing duration of infusion as clinically indicated per investigator discretion.</td></tr>
</table>

NA: not applicable

† Not resolved by the beginning of the next treatment.

‡ May be cold induced.

5.1.2.9 Oxaliplatin-Induced Laryngopharyngeal Dysesthesia

Oxaliplatin has also been associated with laryngopharyngeal dysesthesia, which is an unusual loss of sensation of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm or bronchospasm). Laryngopharyngeal dysesthesia may be induced or exacerbated upon exposure to cold.

Subjects developing laryngopharyngeal dysesthesia should have their oxygen saturation evaluated via a pulse oximeter. If results are normal, reassurance should be provided, a benzodiazepine or other anxiolytic agent should be considered, and the subject should remain for observation in the clinic until the episode has resolved. After resolution, the oxaliplatin infusion may then be continued at one-third the rate.

Because laryngopharyngeal dysesthesia may be associated with the rate of oxaliplatin infusion, subsequent infusions of oxaliplatin should be prolonged from a normal 2-hour infusion to a 6-hour infusion.

Subjects receiving oxaliplatin should avoid consuming cold drinks or ice chips on Day 1 of each cycle, as this may exacerbate oral or throat dysesthesia, as well as laryngopharyngeal dysesthesia. Administration of prophylactic medication such as Mg^{2+}/Ca^{2+} infusions or others is at the discretion of the investigator.

The symptoms and treatments of laryngopharyngeal dysesthesia and platinum HSRs are compared in Table 9.

Table 9 Comparison of the Symptoms and Treatment of Laryngopharyngeal and Platinum Hypersensitivity Reactions

Clinical Symptoms	Laryngopharyngeal Dysesthesia	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Urticaria/rash	Absent	Present
Cold-induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or decreased
Treatment	Reassurance, anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

5.1.2.10 Allergic Reaction to Oxaliplatin

Subjects developing grade 1 or 2 allergic reaction to oxaliplatin should receive premedication according to institutional practice prior to further administration of oxaliplatin. Appropriate premedication should also be given if grade 1 to 2 allergic reaction persists into the next

cycle. Oxaliplatin should be discontinued in subjects developing grade 3 to 4 allergic reactions.

Oxaliplatin should be interrupted pending further investigation in subjects experiencing respiratory symptoms indicative of pulmonary fibrosis such as nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. Oxaliplatin should be permanently discontinued in subjects with confirmed interstitial pulmonary fibrosis.

5.1.2.11 Extravasation of Oxaliplatin

Necrosis has been seen in conjunction with extravasation of oxaliplatin. Subjects with suspected extravasation should have their infusion stopped and the drug administered at another site. Extravasation should be treated according to institutional guidelines.

5.1.3 Treatment Compliance

The dose and schedule of zolbetuximab/placebo and mFOLFOX6 administered to each subject will be recorded on the appropriate eCRF at every cycle. Reasons for dose delay or omission will also be recorded. This information will be used to assess compliance with the treatment.

5.1.4 Criteria for Continuation of Treatment

In case of premature termination, zolbetuximab may be made available to subjects who are still receiving and benefitting from study treatment until a study-defined treatment discontinuation criterion is met.

5.1.4.1 Discontinuation of mFOLFOX6 (all components) and Continuation of IMAB362/Placebo

If a subject discontinues mFOLFOX6 (or components of mFOLFOX6) due to any reason other than disease progression as confirmed by IRC, they may continue on zolbetuximab/placebo at the discretion of the investigator provided that all of the following have been met:

- the subject completed at least 1 cycle (42 days; 3 doses of mFOLFOX6) of mFOLFOX6 treatment;
- the subject will not receive another systemic chemotherapy, immunotherapy, radiotherapy or other treatment intended for antitumor activity; and
- in the investigator's opinion the subject continues to derive clinical benefit with acceptable toxicity.

Subjects should continue to follow the Study Treatment Period Schedule of Assessments [Table 1].

5.1.4.2 Discontinuation of Zolbetuximab/Placebo and Continued of mFOLFOX6 (some or all components)

If zolbetuximab/placebo is permanently discontinued first for reasons other than PD as confirmed by IRC and no other anticancer treatment is started, subjects may continue to receive mFOLFOX6/5-FU and folinic acid until treatment discontinuation criteria are met.

Subjects should continue to follow the Study Treatment Period Schedule of Assessments [Table 1].

5.1.4.3 If Both Zolbetuximab/Placebo and mFOLFOX6 (all components) are discontinued

If both zolbetuximab/placebo and mFOLFOX6 (all components) are discontinued for reasons other than IRC-confirmed radiological PD, the subject should enter the Post-Treatment Follow-Up Period and continue to undergo imaging assessments per Schedule of Assessments [Table 1].

5.1.5 Previous and Concomitant Treatment (Mediation and Non-Medication Therapy

All medications and concomitant treatments administered from the time of full main informed consent through the 90-day safety follow-up visit must be recorded in the eCRF. Documentation will include the medication name, indication, route and dates of administration.

Prohibited Concomitant Treatment

The following are strictly prohibited:

- Sorivudine or analogs (during 5-FU treatment).
- Concurrent nonsteroid systemic immunosuppressive agents (for systemic corticosteroids, see cautionary concomitant treatment below).
- Live vaccines should be avoided during the treatment period in which subject is receiving oxaliplatin or 5-FU and up to 6 months after final oxaliplatin or 5-FU dose. In cases where a live vaccine is needed for COVID-19 prevention and allowed per local regulations, please contact the Medical Monitor for discussion.
- Other systemic chemotherapy, immunotherapy, radiotherapy, herbal medications or other treatments intended for antitumor activity.
    - Palliative radiotherapy for peripheral bone metastases is allowed.
    - For gastric bleeding, palliative radiotherapy is prohibited, but esophagogastroduodenoscopy with epinephrine injection is allowed.
- Investigational products or therapy other than zolbetuximab.

Cautionary Concomitant Treatment

Considerations should be given to avoid or minimize the use of the following concomitant medications, if possible, during zolbetuximab/placebo treatment:

- Systemic corticosteroids, because their impact on the potential efficacy of zolbetuximab is not known.
    - Systemic corticosteroids should be avoided or minimized while subject is on study treatment unless required for management of an emergent medical condition (e.g., severe nausea/vomiting or hypersensitivity reaction).
    - For a subject's first dose of zolbetuximab/placebo, it is recommended that the prophylactic use of corticosteroids be avoided.

  - Inhaled, intranasal, ophthalmic, otic and topically applied steroids are allowed.
- Subjects are allowed to use a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg/day of hydrocortisone or up to 10 mg/day of prednisone), receive a single dose of systemic corticosteroids or receive systemic corticosteroids as pre-medication for radiologic imaging contrast use.
- Administer 5-HT3 blockers with caution in subjects who have or may develop QTc prolongation.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) because of the potential to cause gastric ulcers and covert bleeding.
  - In such cases where NSAID use is necessary, the use of NSAIDs with lower gastric ulcerogenic potential is preferred and concomitant gastric protection with proton pump inhibitors is recommended.

The following should be avoided or used with caution and closely monitored during 5-FU administration:

- CYP2C9 substrates
- Metronidazole and cimetidine
- Anti-epileptic medications (e.g., phenobarbital, phenytoin and primidone)

The following should be avoided or used with caution during oxaliplatin treatment and appropriate monitoring should be conducted:

- Medications known to prolong the QT or QTc interval (refer to https://www.crediblemeds.org for a list of these medications)

Prohibited and cautionary treatments are described in [Appendix 12.4].

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects and will include initials (where permitted), age, date of birth (where permitted), sex, race (where permitted) and ethnicity (where permitted).

5.2.2 Medical History

Medical history includes all significant medical conditions per the judgement of the investigator that have resolved prior to informed consent or are ongoing at the time of full main consent. Details that will be collected include the onset date and recovery date and CTCAE v4.03 grade, if applicable for ongoing conditions.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

A complete medical history of the target disease will be recorded during Screening. This will include the subject's medical condition, date of initial diagnosis, tumor location, and other disease specific information as designated in the eCRF.

5.3 Efficacy Assessments

Radiologic imaging will be evaluated at Screening (within 28 days prior to randomization) and every 9 weeks (± 7 days) counting from C1D1 for the first 54 weeks and then every 12 weeks (± 7 days) thereafter until subject develops radiological disease progression per RECIST 1.1 by IRC or starts other systemic anticancer treatment, whichever comes earlier.

All radiologically evaluable disease (measurable and/or non-measurable), per local assessment, must be documented at Screening and re-assessed at each subsequent radiologic evaluation. Imaging will include CT scans with contrast of the thorax, abdomen, and pelvis. If CT scan with contrast is medically not feasible, MRI may be used for imaging. Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease in bone or brain is suspected, respectively. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change. For randomized subjects, screening images should be sent to the central imaging vendor no later than at time of submission of the first on-treatment imaging. All imaging acquired post randomization will be sent to the central imaging vendor within 7 days of scanning for the blinded independent central assessment of radiological tumor response based on RECIST 1.1 [Eisenhauer et al, 2009]. The investigator should make every effort to immediately submit radiologic assessments for IRC review when PD is suspected. Refer to Imaging Acquisition Guidelines for further detail on scan modality and contrast options.

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg) and radial pulse rate (beats/minute) and temperature, will be obtained and recorded at the times specified in the Schedule of Assessments [Table 1]. All vital sign measurements will be obtained in a consistent manner (sitting or supine) throughout their study participation. Height and weight will be measured using normal institutional standards.

If clinically significant vital sign changes from baseline (pretreatment) are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs, which has medical relevance as deemed by the investigator that could result in an alteration in medical care. For clinically significant vital sign changes, the investigator will continue to monitor the subject until the parameter returns to grade ≤ 1, or to the baseline (pretreatment) value, or until the investigator determines that follow up is no longer medically necessary.

5.4.2 Observation Period following Zolbetuximab/Placebo Infusion

Following the first dose of zolbetuximab/placebo on C1D1, the subject must be observed for 2 hours post zolbetuximab/placebo infusion. The post-infusion observation period can be conducted during the mFOLFOX6 administration. If ≥ grade 2 AEs are observed during infusion or during the post-infusion observation period, subsequent zolbetuximab/placebo infusion times should be extended and subjects should continue to be observed for 2 hours

post zolbetuximab/placebo infusion. If the subject does not develop any ≥ grade 2 AEs, the subject should be observed for 1 hour post-infusion for their subsequent zolbetuximab/placebo infusions. The subject should be instructed to notify site personnel if they develop any AEs during this post-infusion observation time period.

In the event of an IRR with features of anaphylaxis (regardless of grade) or grade 3 or 4 IRR, blood samples for cytokine/chemokine panel and serum total tryptase level (levels typically peak within 3 hours after the onset of symptoms) should be collected once the subject has stabilized for shipment to the central laboratory.

5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study.

Laboratory tests will be performed according to the Schedule of Assessments [Table 1] and must be sent to the central laboratory for analysis.

Eligibility can be determined based on central and/or local laboratory testing.

- The most recent laboratory data must be used to confirm the subject's eligibility. In the case of multiple sample collections within 14 days prior to randomization, the most recent sample collection with available results should be used to determine eligibility.
    - Central labs must be collected and submitted to the central laboratory during the Screening period.
    - If retesting of lab values is necessary to confirm eligibility, local labs can be used without requiring additional sample collection for central laboratory submission.
    - The screening labs used to determine eligibility should be collected within 14 days prior to randomization.
- Laboratory test results (central or local) will be reviewed by the investigator prior to any study treatment. Clinical significance of out of range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician.
- Local laboratory results may be used for treatment decisions; however, central laboratory samples must also be drawn per protocol and sent to the central laboratory, unless otherwise approved by sponsor.
- Central and local labs may be collected up to 48 hours prior to study treatment.
- Holidays and weekends should be taken into account when scheduling these sample collections.
- Additional assessments may be done centrally or locally to monitor AEs or as clinically indicated.

Panel/Assessment	**Parameters to be Analyzed**
Hematology	Hematocrit (Hct) Hemoglobin (Hgb) Red Blood Cell Count (RBC) White Blood Cell Count (WBC) WBC differential Absolute Neutrophil Count (ANC) Platelets Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC)
Biochemistry	Albumin Blood Urea Nitrogen (BUN) Calcium Bicarbonate Chloride Creatinine Glucose Magnesium Phosphate Potassium Sodium Total Bilirubin Total Protein Alanine Aminotransferase (ALT) Alkaline Phosphatase (ALP) Aspartate Aminotransferase (AST) Creatinine Clearance
Urinalysis	Color Clarity/turbidity pH Specific gravity Glucose Ketones Nitrites Leukocyte esterase Bilirubin Urobilinogen Blood Protein RBCs WBCs
Table continued on next page	

Panel/Assessment	Parameters to be Analyzed
Coagulation	Prothrombin time (PT) (sec) Partial Thromboplastin Time (PTT) International normalized ratio (INR)
Thyroid Function Test	Thyroid stimulating hormone (TSH) Free T4 (thyroxine)
Urine Pregnancy Test	Human chorionic gonadotropin (HCG)
Serum Pregnancy Test	Human chorionic gonadotropin (HCG)
Grade 3 or 4 infusion-related reaction (IRR)	Cytokine/Chemokine Panel† Serum total tryptase†
Any reaction with features of anaphylaxis†	Cytokine/Chemokine Panel† Serum Total Tryptase
Dihydropyrimidine dehydrogenase (DPD) deficiency screening†	DPD deficiency alleles

†As applicable

5.4.4 Physical Examination

Physical examinations will be conducted at visits as outlined in the Schedule of Assessments [Table 1]. Each physical exam should include height (at Screening only), weight and ECOG performance status. A full physical exam is required at Screening. The physical exam only needs to be repeated on C1D1 if clinically significant changes from Screening are observed (in the opinion of the investigator). For all cycles, the physical examination, weight and ECOG performance status assessments can be completed up to 48 hours prior to zolbetuximab/placebo administration. Targeted (symptom driven) physical exams should be conducted every 3 weeks on zolbetuximab/placebo visit days. If clinically significant worsening of findings from baseline is noted at any study visit, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings, which has medical relevance that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to grade ≤ 1, or to the baseline condition, or until the investigator determines that follow up is no longer medically necessary.

5.4.5 Electrocardiogram

A single 12-lead ECG will be performed at the time points outlined in the Schedule of Assessments [Table 1].

Prior to performing ECG, subjects should rest in supine position for 10 minutes. When collected on the same day, ECG should be collected prior to pharmacokinetic samples. Additional ECG may be performed based on medical history and investigator medical judgement. ECGs will be read locally. Clinically significant findings should be recorded as an AE.

5.4.6 Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status. Refer to [Appendix 12.8].

5.5 Adverse Events and Other Safety Aspects

AEs and SAEs, regardless of causality will be collected from the time of full main informed consent through 90 days following the last dose of zolbetuximab/placebo and mFOLFOX6 (all components).

AEs will be documented at each clinic visit, but can be collected at any time. Any AE that meets the definition of an SAE will also be reported on a separate form to the sponsor.

5.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent and will be collected until 90 days after the last dose of study treatment or the subject is determined to be a screen failure.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

5.5.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, clinical chemistry or urinalysis) or other safety assessment (e.g., ECGs, radiology scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgement of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject’s condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in total bilirubin that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an(S)AE:

- Disease Progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data as outlined in [Section 5.3 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study treatment and the event, it should be reported as an (S)AE. All deaths up to 90 days after the last dose of study drug must be reported as an SAE, even if attributed to disease progression.
- Disease progression can be considered as the worsening of a subject's condition attributable to Gastric or GEJ cancer. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastases to the primary cancer under study should be considered as disease progression not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study.

5.5.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.
- Other medically important events (defined in paragraph below)

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.5.2.1 Important Medical Events

If an AE occurs that the sponsor determines to be an Important Medical Event, additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested.

Progression of Gastric or GEJ cancer, including signs and symptoms of progression, should not be reported as an SAE unless it results in death within 90 days of the last dose of study treatment. For progression-related death reported as an SAE, there should be available immediate cause of death reported as the event term. “Death due to disease progression” should be recorded as the AE term only when the cause of death cannot be otherwise determined.

5.5.3 Criteria for Causal Relationship to Study Treatment

A medically-qualified investigator is obligated to assess the relationship between each study treatment and each occurrence of each (S)AE. This medically-qualified investigator will use medical judgement, as well as the RSI to determine the relationship. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The medically qualified investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the study treatment and each (S)AE will be assessed by answering ‘**yes**’ or ‘**no**’ to the question “**Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment**”.

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a ‘reasonable possibility’ that an (S)AE may have been caused by the study treatment (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study treatment and (S)AE onset and/or resolution. Has the subject actually received the study treatment? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study treatment?

- Plausibility; i.e., could the event have been caused by the study treatment? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
    - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study treatment (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study treatment exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the medically-qualified investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-CTCAE v4.03 guidelines. The items that are not stipulated in the NCI-CTCAE v4.03 will be assessed according to the criteria below and entered into the eCRF.

Grade	Assessment Standard
1-Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events

The collection of AEs and the expedited reporting of SAEs will start following receipt of the signed full main informed consent and will continue to until 90 days after the last dose of study treatment or the subject is determined to be a screen failure.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit a SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data as well as the investigator causality assessment including the explanation for the causality assessment.

If the SAE is associated with emergency unblinding as outlined in Section 4.7.4 Breaking the Treatment Code for Emergency this is to be recorded on the SAE worksheet. Within the SAE worksheet, the investigator is to include when unblinding took place in association with the SAE.

***JAPAN SITES ONLY*:** In the case of a SAE, the investigator or sub-investigator must report to the head of the study site and must contact the sponsor by email or fax immediately (within 24 hours of awareness). The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to the sponsor by email or fax immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, the sponsor should be informed by phone.

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE and Special Situations Worksheet to:

Astellas Pharma Global Development, Inc.
Pharmacovigilance
North American Fax: +1-888-396-3750
(North America Alternate Fax: +1-847-317-1241)

International Fax: +44-800-471-5263
Email: safety-us@astellas.com

UNIQUE TO JAPAN REGION*:* JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE and Special Situations Worksheet to:

PAREXEL International
Fax number: 03-6888-5798

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Study Physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification (***UNIQUE TO JAPAN REGION*****:** within 2 days for the initial notification).

Full details of the SAE or Special Situation should be recorded on the medical records, SAE or Special Situation Worksheet and on the (e)CRF.

The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness criteria),
- Causal relationship to the study treatment (including reason), and
- The drug provided (if any). Note: blinded regimen is also an option.

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting) according to current local/regional regulatory requirements in participating countries. The sponsor or sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports, Council for International Organizations of Medical Sciences I Form) to Competent Authorities (CA) and concerned Ethics Committee per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations (e.g., EU, (e)CTD, FDA) where required. Documentation of the submission to and receipt by the IRB/ local IEC of expedited safety reports should be retained by the study site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study treatment of all SUSARs, which require submission per local requirements IRB/local IEC/ head of the study site (as applicable).

The heads of the study sites (if applicable) and investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol defined AE collection period [see Section 5.5.1 Definition of Adverse Event], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study treatment or study participation, the investigator must promptly notify the sponsor.

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in [Appendix 12.6 Common Serious Adverse Events] for reference. The list does NOT change the investigator's reporting obligations, nor his obligations to perform a causality assessment, or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs" as specified in [Appendix 12.6 Common Serious Adverse Events]. The sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.8 Adverse Events of Special Interest

In case of zolbetuximab induced nausea, vomiting or hypersensitivity/IRR, infusion rate of zolbetuximab/placebo may be reduced or infusion paused or discontinued based on investigator's clinical judgement about severity of toxicity and local standard of care. See [Section 5.1.2 Study Treatment Dose Modifications, Delays and Interruption] and the Pharmacy Manual and Infusion Guidelines.

If the AEs of interest are classified as serious, they are to be collected via the SAE worksheet and reported within 24 hours as described in [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.9 Special Situations

Certain Special Situations observed in association with the study treatment(s), such as incorrect administration (e.g., wrong dose of study treatment, comparator or background therapy) are collected in the eCRF, as Protocol Deviations per [Section 8.2 Major Protocol Deviations] or may require special reporting, as described below. These Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in the eCRF. If the AE meets the

definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the Special Situation worksheet.

The Special Situations are:

- Pregnancy
- Medication error, Overdose and "Off label use"
- Misuse/abuse
- Occupational exposure
- (Suspicion of) Transmission of infectious agent
- Suspected Drug-Drug interaction

5.5.9.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs, or if a partner of a male subject becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in [Section 5.5.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form and in the eCRF.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per [Section 5.5.5 Reporting of Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.5.9.2 Medication Error, Overdose and "Off-Label Use"

If a Medication Error, Overdose or "Off label Use" (i.e., use outside of what is stated in the protocol) is suspected [refer to Section 8.2 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose or "Off-Label Use".

There is no antidote for overdose of the study drug. In the event of suspected zolbetuximab overdose, the subject should receive supportive care and monitoring (including, but not limited to, inpatient hospitalization). The Medical Monitor should be contacted as applicable.

In the event of suspected mFOLFOX6 overdose, refer to the approved package insert, SPC or local product information supplied by the manufacturer for each agent.

5.5.9.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor/delegated contract research organization (CRO) by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.5.9.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the study drug(s) of site staff whilst preparing it for administration to the subject) to the study drug(s) occurs, the investigator must forward the Special Situation worksheet to the sponsor/delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.5.9.5 Suspected Drug-Drug Interaction

If a suspected drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor/delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue in the clinical study.

UNIQUE TO JAPAN REGION:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Section 12.1.4.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information.]
2. In addition to the above item (1), when the head of the study site receives the revisions of the IB, protocol or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB these documents should be sent to the IRB.

5.5.11 Urgent Safety Measures

An Urgent Safety Measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant CA, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety, product or procedure related.

5.5.12 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the Astellas Study Physician and/or – unique for JP region – Astellas team member (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the patients. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify CA and central Ethics Committee within the timelines required per current local regulations, and will inform the investigators as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

Serum concentrations of zolbetuximab will be measured. Samples will be collected as outlined in the Schedule of Assessments. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory using validated analytical methods. Please refer to the Laboratory Manual for more detailed information.

Samples remaining after pharmacokinetic assessments may be used for additional biomarker analysis described in [Section 5.7.1 Biomarkers].

5.7 Other Measurements, Assessments or Methods

5.7.1 Biomarkers

Tumor tissue and blood/serum/plasma samples described in [Sections 5.7.2 Blood, Serum and Plasma Samples and 5.7.3 Tumor Tissue Samples] may be used for research purposes as allowed per local policy to identify genomic and/or other biomarkers that may be associated with clinical outcome or dynamic changes associated with zolbetuximab treatment (in terms of dose, safety, tolerability and efficacy). Since the identification of exploratory biomarkers that correlate with the efficacy or safety of zolbetuximab treatment may continue to evolve as new findings becomes available, additional analyses related to zolbetuximab activity on tumor signaling pathways or clinical outcomes may be conducted as allowed per local policy. Tumor tissue and blood/serum samples remaining after the specified biomarker assessments (e.g., aliquots of tumor cell RNA or DNA) may be used for re-testing, additional analyses as defined above or developing, and validating assays related to prediction of response or dynamic changes associated with zolbetuximab treatment. The tumor tissue and blood/serum/plasma samples (e.g., aliquots of tumor cell RNA or DNA, peripheral blood mononuclear cells) will be stored at the study sponsors' facility or a contract laboratory facility for up to 15 years after database closure, at which time the samples will be destroyed. The procedures for the collection, handling and shipping of laboratory samples being submitted to the central laboratory will be specified in a laboratory manual.

5.7.2 Blood, Serum and Plasma Samples

Blood, serum and plasma samples will be collected as allowed per local policy according to the Schedule of Assessments [Table 1] for exploratory biomarker measurements. Blood, serum and plasma samples may be analyzed for biomarkers including but not limited to chemokines, cytokines, CDC activation, circulating DNA soluble factors and genetic markers.

5.7.3 Tumor Tissue Samples

FFPE tumor tissue samples will be obtained for all subjects and sent for central IHC testing to evaluate for CLDN18.2, and HER2 status if a previously documented HER2 test result is not available. Tissue from the primary site is preferred; however, if a metastatic site is used (excluding bone metastasis), the sample should be gastric or GEJ in origin. Archival tumor tissue is preferred, but if the specimen is insufficient or unavailable, a biopsy may be

performed to obtain a primary tumor tissue or tumor tissue from metastatic site (excluding bone metastasis). Sponsor preapproval is required when a biopsy procedure is needed for the sole purpose of determining study eligibility. Optional post-progression tumor tissue sample for exploratory biomarker analysis may be collected, as allowed per local policy following IRC confirmation of disease progression and prior to initiation of subsequent anticancer therapy for subjects who sign a separate ICF. Tumor specimens may be analyzed for exploratory biomarkers including but not limited to CLDN18.2 expression, immune cells, genetic markers and gene/protein expression, as allowed per local policy.

The investigator, in consultation with other specialists, as needed (e.g., radiology staff) will assess the risk associated with obtaining a tumor tissue sample and determine if the subject is an appropriate candidate for the procedure. Biopsies should be obtained in accordance with institutional policies/guidelines to minimize risk. Procedures requiring general anesthesia should not be performed to obtain a tumor tissue sample; however, if a surgical procedure under general anesthesia is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

Tumor Tissue Requirements

Visit	Tumor Tissue Requirement
Screening	A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum* of 15 FFPE unstained slides are required, as allowed per local policy. If local HER2 results are available, a minimum* of 12 slides are required along with the pathology report/documented test results. If local HER2 results are unavailable, follow guidance above.
Post-Progression (optional)	A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum* of 15 FFPE unstained slides are required, as allowed per local policy.

FFPE: formalin-fixed paraffin embedded; HER2: human epidermal growth factor receptor 2

*If the required minimum number of slides is not able to be submitted, sponsor notification and approval is required.

5.7.4 Immunogenicity Assessment (ADA)

Serum samples to assess the formation of ADAs against zolbetuximab will be collected as outlined in the Schedule of Assessments [Table 1]. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a sponsor designated analytical laboratory using validated analytical methods. Please refer to the Laboratory Manual for more detailed information.

Samples remaining after immunogenicity assessments may be used for additional biomarker analysis, as allowed per local policy, as described in [Section 5.7.1 Biomarkers].

5.7.5 Optional Samples for Future Pharmacogenomic Analysis

For subjects who signed a separate ICF, an optional whole blood sample for pharmacogenomics (PGx) will be collected at C1D1 prior to first study drug administration, as allowed per local policy. PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety

issues. A sample of whole blood for possible retrospective PGx analysis will be collected and processed, as allowed per local policy. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to a sponsor-designated analytical storage laboratory. Please refer to the Laboratory Manual for more detailed information.

See [Appendix 12.7, Retrospective PGx Sub-study] for further details on the banking procedures.

5.7.6 Electronic Clinical Outcome Assessments (HRQoL and HRU)

Subjects will be asked to complete HRQoL and HRU questionnaires as specified in the Schedule of Assessments [Table 1]. The electronic Clinical Outcomes Assessment (eCOA) questionnaires should be completed by the subject at Screening (except HRU), on day 1 and day 22 of each cycle (or up to 48 hours) before any antiemetic or drug treatment and before the disease status is discussed with the subject using the electronic device provided. When completion by the subject is not possible, the questionnaires may be administered to the subject by site personnel using the electronic tablet device. For subjects with low literacy or situations where required translation is not available, please contact the sponsor for further guidance. Assessments will also be collected at study treatment discontinuation and 30 and 90 days post zolbetuximab/placebo treatment. HRQoL and HRU questionnaires are not required at mFOLFOX6 dosing visits (if different from zolbetuximab/placebo dosing visit), mFOLFOX6 treatment discontinuation, 30 day safety follow-up and 90 day safety follow-up visits. A combined visit can be completed if zolbetuximab/placebo and all components of mFOLFOX6 are discontinued on the same day and HRQoL and HRU questionnaires should be completed for a combined visit. HRQoL will be measured by EORTC QLQ-C30, QLQ-OG25, GP and the EQ5D-5L.

5.7.6.1 Quality of Life Questionnaire C30 (QLQ-C30)

The EORTC-QLQ-C30 is a 30-item cancer-specific instrument consisting of 5 functional scales (physical, role, emotional, social and cognitive), 9 symptom scales/items (fatigue, nausea/vomiting, general pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) and a global health status scale. For functional scales, higher scores indicate better functioning, while for symptom scales/items, higher scores indicate worse symptoms.

5.7.6.2 Oesophago-Gastric Module 25 (OG-25)

The EORTC QLQ-OG25 questionnaire is a 25-item instrument that evaluates gastric and GEJ cancer-specific symptoms. This module consists of 6 scales: dysphagia (3 items), eating restrictions (4 items), reflux (2 items), odynophagia (2 items), pain and discomfort (2 items) and anxiety (2 items), as well as 10 single items: eating in front of others, dry mouth, trouble with taste, body image, trouble swallowing saliva, choked when swallowing, trouble with coughing, trouble talking, weight loss and hair loss. For symptom scales/items, higher scores indicate worse symptoms.

5.7.6.3 Global Pain (GP)

The GP instrument is a single assessment of overall pain.

5.7.6.4 EuroQOL Five Dimensions Questionnaire (EQ-5D-5L)

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome consisting of 6 items that cover 5 main domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a general visual analog scale for health status.

5.7.6.5 Health Resource Utilization

The HRU questionnaire is used to assess the number of office visits, hospital stays, and other healthcare resource utilization that occur outside of the clinical trial.

5.8 Total Amount of Blood

The total amount of blood collected for study assessments for each subject will vary depending on how long they stay on treatment.

At any time during the study, if any laboratory abnormalities are found for a subject or for disease assessment, additional blood may be drawn for monitoring.

Additional blood beyond standard monitoring that will be drawn for this study will include draws for eligibility assessment, hematology, chemistry, and coagulation at specific study defined time points, pharmacokinetics, and biomarker sampling.

The maximum amount of blood collected is approximately 81 mL in Cycle 1, and less in subsequent cycles.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s) From Study Treatment

A subject who enrolled in the study and for whom study treatment (zolbetuximab/placebo and all components mFOLFOX6) is permanently discontinued for any reason will be assessed as having met study treatment discontinuation criteria.

As survival is the secondary end-point of the study, all subjects will be followed for survival after meeting study treatment discontinuation criteria unless the subject withdraws consent or is considered lost to follow-up after repeated attempts to contact or if the sponsor discontinues the study.

A subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

A subject will be discontinued from study treatment (zolbetuximab/placebo and all components mFOLFOX6) if any of the following occur:

- Investigator determines it is in the subject’s best interest to discontinue study treatment

- Subject develops radiological disease progression per RECIST 1.1 criteria based on assessment by IRC.
    - If the investigator believes that the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study treatment until an additional radiologic assessment is completed (≤ 9 weeks from previous radiologic assessment).
        - If the additional radiologic assessment by IRC indicates PD per RECIST 1.1 then the subject must be discontinued from study treatment.
        - If the additional radiologic assessment by IRC does not confirm the initial assessment of PD, the subject may continue study treatment.
- Subject develops clinical progression per investigator assessment and radiologic assessment is not medically feasible to confirm radiologic progression due to the subject's condition.
- Subject starts another systemic anticancer treatment chemotherapy, immunotherapy, radiotherapy or other treatment intended for antitumor activity.
- Subject starts another investigational agent or device
- Subject develops unacceptable toxicity.
- Subject has a delay of study treatment (zolbetuximab/placebo and all components mFOLFOX6) for > 28 days from when the next study treatment was scheduled to be administered (> 49 days from when the last dose of zolbetuximab/placebo and > 42 days from when the last dose of mFOLFOX began).
- Subject develops inter-current illness that the investigator determines may jeopardize the subject's safety if the subject continues to receive study treatment.
- Female subject becomes pregnant.
- Significant deviation from the protocol or eligibility criteria as determined by the sponsor.
- Subject declines further treatment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject is noncompliant with the protocol based on investigator or Medical Monitor assessment.

Note: If a subject discontinues mFOLFOX6 and/or zolbetuximab/placebo due to any reason other than IRC confirmed disease progression (and is not receiving any other anticancer therapy), the subject must be followed according to the protocol-specified radiologic assessment schedule until radiological disease progression per RECIST 1.1 criteria is confirmed by IRC assessment.

Study Discontinuation Criteria

All subjects should remain in the study through the Survival Follow-up Period (OS is a key secondary study endpoint). A subject will be discontinued from the Post-Treatment, Long Term and Survival Follow-up Periods if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject
- Death (from any cause)
- Study termination by the sponsor

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor and, ***SPECIFIC TO SITES IN JAPAN***, the head of the study site must also be informed immediately.

6.3 Discontinuation of the Study

If the study is prematurely terminated or suspended the sponsor or designee shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The study may also be terminated if it is not possible for the sponsor to make a necessary adjustment to the maximum insurance sum as required by local law/regulation.

In case of premature study termination, zolbetuximab may be made available to subjects who are still receiving and benefitting from study treatment until a study defined treatment discontinuation criterion is met.

7 STATISTICAL METHODOLOGY

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the randomization of the first subject. Any changes from the analyses planned in SAP will be justified in the clinical study report.

Prior to database lock, a final review of data and tables, listings and figures meeting (final DRM) will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, continuous data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous variables, and frequency and percentage for categorical variables.

Baseline will be defined as the last observation prior to first dose, unless otherwise specified.

7.1 Sample Size

Approximately 550 subjects will be randomized in a 1:1 ratio to receive zolbetuximab in combination with mFOLFOX6 chemotherapy (Arm A) or placebo in combination with mFOLFOX6 chemotherapy (Arm B). The planned 300 PFS events during the study will provide 93.4% power to detect a difference in PFS between Arm A (zolbetuximab + mFOLFOX6) with the assumption of 9 months median PFS time and Arm B (placebo + mFOLFOX6) with the assumption of 6 months median PFS time (hazard ratio = 0.67) at the overall 1-sided 0.025 significance level. Similarly, the planned 396 OS events during the study will provide 81% power to detect a difference in OS between Arm A (zolbetuximab + mFOLFOX6) with the assumption of 14.7 months median survival time and Arm B (placebo + mFOLFOX6) with the assumption of 11 months median survival time (hazard ratio = 0.75) at the overall 1-sided 0.025 significance level.

7.2 Analysis Sets

The allocation of subjects to analysis sets will be determined prior to database hard-lock. For each treatment group, the number and percentage of subjects will be characterized for all randomized subjects and by each analysis set.

7.2.1 Full Analysis Set

The FAS will consist of all subjects who are randomized to 1 of the treatment arms. Subjects will be analyzed according to the treatment arm to which they were randomized. The FAS will be used for description of baseline characteristics and all efficacy analyses.

7.2.2 Safety Analysis Set

The safety analysis set (SAF) will consist of all subjects who received at least 1 dose of any study drug (zolbetuximab/placebo/mFOLFOX6). The safety analysis set will be used for all safety analyses. Subjects would be analyzed according to the actual treatment they received.

7.2.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF for which at least 1 concentration data is available. Additional subjects may be excluded from the PKAS at the discretion of the Pharmacokineticist. The PKAS would be used for description of pharmacokinetic data.

7.3 Demographics and Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group and overall for FAS and SAF.

7.3.1 Subject Disposition

The number and percentage of subjects who discontinued treatment and reasons for treatment discontinuation will be presented for FAS by treatment group and overall. Similar tables for subjects who do not have a PFS event and subjects who do not have observed death will also

be presented. All disposition details and dates of first and last evaluations for each subject will be listed.

7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be presented in a listing.

All previous and concomitant medications will be presented in a listing. The frequency of concomitant medications (prescription, over-the-counter, and nutritional supplements) will be summarized. Any component of mFOLFOX6 is not considered concomitant medications.

7.3.3 Medical History

Medical history for each subject will be presented in a listing and summarized.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS. The interpretation of results from statistical tests will be primarily based on the FAS. All randomized subjects will be analyzed according to the treatment to which they are randomized.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary endpoint is PFS assessed by the blinded IRC. For each subject, PFS is defined as the time from the date of randomization until the date of radiological disease progression (i.e., PFS) assessed by IRC, or until death due to any cause, whichever is earlier. If a subject has neither progressed nor died, the subject will be censored at the date of last radiological assessment. Subjects who receive new anticancer therapy before radiological progression will be censored at the date of the last radiological assessment before the new anticancer therapy started. If progression or death occurs after missing 2 or more scheduled radiological assessments, the subject will be censored at the date of last radiological assessment or at the date of randomization if no post-baseline radiological assessment is available.

The primary analysis will be performed when approximately 300 PFS events have been observed.

The distribution of PFS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using log-rank test stratified by:

- Region (Asia vs Non-Asia)
- Number of organs with metastatic sites (0 to 2 vs ≥ 3)
- Prior gastrectomy (Yes or No)

The hypothesis testing on the primary analysis will be performed at an overall 1-sided 0.025 significance level to test the null hypothesis that PFS is not prolonged in Arm A compared to Arm B versus the alternative hypothesis that PFS is prolonged in Arm A compared to Arm B.

In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI.

The primary analysis will be performed using the FAS.

7.4.1.2 Sensitivity Analyses

Sensitivity analyses with different censoring rules will be described in the SAP.

7.4.1.3 Subgroup Analysis

The analysis described in [Section 7.4.1.1 Primary Analysis] will be conducted in the subgroups using the FAS. Subgroups defined by baseline factors will be described in the SAP.

Forest plot will be presented to illustrate the strength of treatment effects across subgroups.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Overall Survival

A key secondary endpoint OS is defined as the time from the date of randomization until the documented date of death from any cause. All events of death will be included, regardless of whether the event occurred while the subject is still taking study drug or after the subject discontinue study drug. Subjects who are still alive at the time of analysis will be censored at the last day known to be alive.

The distribution of OS will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by the same stratification factors used for PFS analysis. To maintain the overall Type I error rate at the 0.025 significance level, the hypothesis testing on OS will be performed only if the null hypothesis on the primary analysis is rejected at the overall 1-sided 0.025 significance level. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI.

7.4.2.2 PF, OG25-Pain, and GHS/QoL Scores

A key secondary endpoint, TTCD, is defined for the following 3 HRQoL domains: physical functioning (PF) and Global Health Status/Quality of Life (GHS/QoL) as collected in the EORTC QLQ-C30, and abdominal pain and discomfort (OG25-Pain) as collected in the EORTC QLQ-OG25). TTCD is defined as the time from the date of randomization until the date of first clinically meaningful deterioration that is confirmed at a next scheduled assessment or followed by drop-out resulting in missing data.

Clinically meaningful deterioration will be defined if a subject's change from baseline exceeds a pre-specified threshold denoting a clinically meaningful change. While clinically meaningful thresholds have been derived for EORTC QLQ-30 for some domains (e.g., 10 for GHS/QoL in Osoba 1998), an appropriate threshold for this population and for all domains of interest will be derived using the study's data. A separate analysis plan will be developed where methods for the estimation of the clinically meaningful threshold will be defined in detail and signed off before database lock. The execution of these analysis and derivation of the threshold value to be used in the TTCD analysis will also be performed before database

lock, and the resulting value will be inserted in the clinical SAP in a last amendment again before the study is unblinded.

Subjects who did not experience a confirmed deterioration will be censored at the last eCOA assessment. Subjects who have no baseline or post-baseline assessment, or are not able to show deterioration due to their baseline value will be censored at randomization. For example, if a subject has a baseline GHS/QoL value of 5 and the clinically meaningful threshold proves to be 8, then this subject will be censored at baseline. Death or disease progression will not be considered as an event.

Similarly to PFS and OS endpoints, the distribution of TTCD will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by the same stratification factors used for PFS and OS analysis. To maintain the overall Type I error rate at the 0.025 significance level, the hypothesis testing on TTCD will be performed only if the null hypothesis on the OS is rejected at the overall 1-sided 0.025 significance level. Specifically, if the null hypothesis on the OS is rejected at the overall 1-sided 0.025 significance level, then the TTCD will be tested using the gatekeeping procedure with the following order:

1. Non-inferiority testing for TTCD in PF at 0.025 significance level
2. Non-inferiority testing for TTCD in OG25-Pain at 0.025 significance level
3. Non-inferiority testing for TTCD in GHS/QoL at 0.025 significance level
4. Superiority testing for TTCD in PF at 0.025 significance level
5. Superiority testing for TTCD in OG25-PA at 0.025 significance level
6. Superiority testing for TTCD in GHS/QoL at 0.025 significance level

A stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI for the three time-to-event eCOA endpoints.

7.4.2.3 Objective Response Rate

Best overall response (BOR) is determined once all tumor response data for the subject is available. Subjects will be classified by BOR on study as outlined in RECIST V1.1 criteria. For BOR of SD, SD must be documented as present at least once after study entry and at least 8 weeks after first dose.

The ORR is defined as the proportion of subjects with a BOR of complete response (CR) or partial response (PR) based on IRC per RECIST V1.1.

The comparison of ORR between Arm A and Arm B will be performed using stratified Cochran-Mantel-Haenszel (CMH) test with the same stratification factor used for the PFS analysis. In addition, ORR for each arm will be estimated and corresponding 95% CI will be constructed.

In addition, percent of subjects with CR will be summarized.

7.4.2.4 Duration of Response

DOR is defined as the time from the date of the first response of CR or PR (whichever is first recorded) as assessed by IRC to the date of radiological progression or death, whichever is earlier. If a subject has not progressed, the subject will be censored at the date of last radiological assessment or at the date of first CR/PR if no post-baseline radiological assessment is available. Other censoring used for the PFS analysis will apply to DOR too.

The distribution of DOR will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using the log-rank test stratified by the same stratification factors used for the PFS analysis. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI.

7.4.2.5 Health-Related Quality of Life

HRQoL endpoints will be summarized by descriptive statistics with respect to change from baseline for the FAS for each treatment arm. Completion rate for each questionnaire will be summarized by time point. Additional analyses will be described in the SAP.

7.4.3 Analysis of Exploratory Endpoints

7.4.3.1 Time to Progression

TTP is defined as the time from the date of randomization until the date of PD (per RECIST 1.1 by IRC). TTP does not include deaths as event. For deaths before the first documented PD by IRC, subjects will be censored at the time of last radiological assessment. The TPP analysis assumes the pre-PD deaths are not related to tumor progression and estimates the TTP for pre-PD deaths if the subjects had not die. Kaplan-Meier and log-rank methods will be applied to TTP endpoint.

7.4.3.2 Progression Free Survival After Subsequent Therapy (PFS2)

PFS2 is defined as the time from the date of randomization until the date of PD (per investigator) following subsequent anticancer therapy, death from any cause or start of any other anticancer therapy, whichever is earliest. In cases where PFS2 cannot be reliably determined, discontinuation of subsequent anticancer treatment may be used as the event date. Otherwise, subjects will be censored. Subjects who are alive and for whom a PFS2 event date has not been observed should be censored at the last time known to be alive and without second objective disease progression.

The distribution of PFS2 will be estimated for each treatment arm using Kaplan-Meier methodology and compared between Arm A and Arm B using stratified log-rank test with the same stratification factors used for the PFS analysis. In addition, stratified Cox proportional hazard model will be used to estimate the hazard ratio and the corresponding 95% CI.

7.4.3.3 Disease Control Rate

The DCR is defined as the proportion of subjects with a BOR of SD, CR or PR based on RECIST 1.1 by IRC.

The comparison of DCR between Arm A and Arm B will be performed using CMH test with the same stratification factor used for PFS analysis. In addition, DCR for each arm will be estimated and corresponding 95% CI will be constructed.

7.4.3.4 Biomarkers

Biomarkers may be summarized graphically or descriptively, and summary statistics may be tabulated. Associations between biomarkers and clinical (e.g., efficacy, safety or pharmacodynamics, pharmacokinetics) measures may be performed on subjects who have sufficient baseline and on-study measurements to provide interpretable results for specific parameters. Additional post-hoc statistical analyses may be outlined in the SAP.

7.4.3.5 Health Resource Utilization

HRU variables will be summarized for each treatment arm.

7.5 Analysis of Safety

All treated subjects will be analyzed according to the treatment they received.

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using NCI-CTCAE v4.03.

Treatment emergent adverse event (TEAE) is defined as an AE observed after starting administration of the study treatment and within 30 days after the last dose of study treatment. Late SAE and/or AE is defined as (S)AE that is collected after 30 days post last dose of study drug.

A study drug-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator.

AEs of special interest described in [Section 5.5.8 Adverse Events of Special Interest] will be summarized.

The number and percentage of AEs, SAEs, AEs leading to interruption/ discontinuation, AEs leading to death and AEs related to study drug will be summarized by SOC, preferred term for SAF. The number and percentage of AEs by toxicity grade will also be summarized. Late (S)AEs will be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline for subjects in the SAF by treatment group and time point.

Incidences of subjects with shifts from baseline to worse grade based on NCI CTCAE v4.03 in laboratory tests will be summarized by treatment group, time point and grade.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by treatment group and time point.

7.5.4 Routine 12-lead Electrocardiograms

The 12-lead ECG results will be summarized by treatment group and time point.

7.5.5 Eastern Cooperative Oncology Group Performance Status

Summary statistics (number and percent of subjects) for each category of the ECOG performance status at each assessment will be provided. The change from baseline to final visit or early termination will also be summarized. Negative change scores indicate an improvement. Positive scores indicate a decline in performance.

7.6 Analysis of Pharmacokinetics

Descriptive statistics (e.g., number of subjects, mean, standard deviation, minimum, median, maximum, coefficient of variation [CV], geometric mean, and geometric CV) will be provided.

7.6.1 Serum Concentrations

Serum concentrations of zolbetuximab will be listed and summarized using descriptive statistics by scheduled time point. Box and whisker plots of trough concentrations against cycle and dosing day will be provided.

7.6.2 Immunogenicity

Immunogenicity of zolbetuximab will be summarized using the frequency of ADA positive subjects. The potential relationship between zolbetuximab immunogenicity and zolbetuximab pharmacokinetics, efficacy, safety profile in subjects may be assessed.

Additional model-based analyses may be performed and reported separately.

7.7 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.2 Major Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing.

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

To evaluate whether zolbetuximab + mFOLFOX6 (Arm A) is beneficial compared to the concurrent placebo + mFOLFOX6 (Arm B) while the study is ongoing, a formal OS interim analysis is planned when the final PFS analysis occurs with the pre-specified number of PFS events. A group sequential design using the O'Brien-Fleming type alpha-spending function [Lan & DeMets, 1983] will be utilized to control the overall 1-sided 0.025 significance level (East®) for the OS analysis.

The IDMC may recommend terminating the trial for favorable or unfavorable results at the formal efficacy interim analysis using PFS and OS. If the PFS is not significant at 0.025 1-sided alpha, the trial may be terminated for failure. In the case of favorable results, the

1-sided significance level for superiority is 0.0082, assuming about 72% of the target number of OS events is obtained, for the interim OS analysis and 0.0225 for the final OS analysis (Note: The OS significance level will be adjusted depending on the number of OS events at the time of interim analysis). If the 1-sided P value of the interim OS analysis is less than the significance level (and PFS is also significant at 1-sided 0.025 alpha), the IDMC may recommend terminating the trial for success. If the study is not stopped after the interim analysis, a final OS analysis will occur after 100% of the planned death events have been observed.

The interim OS analysis will be conducted by an Independent Data Analysis Center for IDMC. In addition, safety data reviews during the trial will be conducted by the IDMC on a periodic basis. For example, the IDMC will have its first safety data review 6 weeks after the 40th subject has been randomized and on study drug for 1 cycle (6 weeks) and meetings will be conducted regularly thereafter, as determined by the IDMC.

The full procedures for IDMC safety review will be described in a separate IDMC Charter.

The analysis for the eCOA endpoints will be performed as the final analysis once OS is significant either at the interim OR or at final OS anlaysis hence there is no interim analysis planned for eCOA endpoints.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Imputation for missing data, if applicable, will be addressed in the SAP.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. These documents should be appropriately maintained by the site.

Local laboratory results may be used for treatment decisions; however, central laboratory samples must also be drawn per protocol and send to the central laboratory, unless otherwise approved by sponsor. Central Laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The Central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

Imaging results are read by a central imaging laboratory. Central imaging data will be transferred electronically to the sponsor or designee at predefined intervals during the study.

The central imaging laboratory will provide the sponsor or designee with a complete and clean copy of the data.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

8.1.1.1 Collection of Data Via Electronic Source

All procedures conducted under the protocol must be documented. For screen failures, the minimum demographic data (sex, birth date, race and informed consent date), outcome of eligibility assessment (inclusion and exclusion criteria), reason for screen failure and AEs details must be documented.

The investigator or designee will be responsible for eCRF completion and for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment and/or drug accountability.

Electronic data sources and any supporting documents should be available for review/retrieval by the sponsor/designee at any given time.

Study monitors will perform ongoing source data review to confirm that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

8.1.1.2 Electronic Clinical Outcomes Assessment

eCOA assessments will be performed according to the Schedule of Assessments [Table 1]. Subject HRQoL and HRU questionnaires will be completed by the subject or, if not possible, administered to the subject by site personnel on an electronic tablet device for subject visits. The subject questionnaire responses captured on the electronic device will be transferred to the eCOA vendor's central portal (web portal). The investigator or site designee should review the questionnaire data on the web portal for correct completion while the subject is at the site. The questionnaire data will be transferred electronically to sponsor or designee at predefined intervals during the study. Sponsor/CRO staff also have access to the vendor web portal for continuous review of the data and access to reports. The vendor will provide sponsor or designee with a complete and clean copy of the data.

For further details please refer to the eCOA guidelines/manual (e.g., ERT Site Guide to eCOA Product).

8.2 Major Protocol Deviations

A major protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. All deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety of the subject to determine subject continuation in the study.

Major protocol deviation criteria will be summarized at the end of the study.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file.

9 END OF TRIAL IN ALL PARTICIPATING COUNTRIES

The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments [Table 1] for the last study participant in the study.

Study completion is defined as the conclusion of data collection for the defined study endpoints. The study may be closed within a participating country per local regulations once the study has completed and if all subjects enrolled in the country are no longer receiving study treatment. In addition, the sponsor may prematurely terminate the study for reasonable cause at any time.

10 STUDY ORGANIZATION

10.1 Independent Data Monitoring Committee

An IDMC will evaluate the unblinded safety data of subjects enrolled on a periodic basis during this study. IDMC members will be clinicians with expertise in gastric cancer trials and a statistician and are not investigators participating in this trial or Astellas employees. A separate charter will outline the activities of this committee.

10.2 Other Study Organization

SPECIFIC TO SITES IN JAPAN: The Japan site contact list is kept as a separate attachment to the protocol.

11 REFERENCES

Amiri M, Janssen F, Kunst AE. The decline in stomach cancer mortality: exploration of future trends in seven European countries. Eur J Epidemiol. 2011;26:23-8.

Bang Y, Chung H, Xu J, Lordick F, Sawaki A, Al-Sakaff N, et al. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. J Clin Oncol. 2009;27(155):4556.

Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687-97.

Cancer Fact Sheet. World Health Organization; February 2018.

CYRAMZA Prescribing Information. Indianapolis, IN: Eli Lilly and Company; 2017.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383:31-39.

Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009.

Gunzel D, Yu SL. Claudins of the modulation of tight junction permeability. Physiol. Rev. 2013;93(2):525-69.

HERCEPTIN (trastuzumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 2016.

Karanjawala ZE, Illei PB, Ashfaq R, Infante JR, Murphy K, Pandey A, et al. New markers of pancreatic cancer identified through differential gene expression analyses: claudin 18 and annexin A8. Am J Surg Pathol. 2008;32:188-196.

Lan KKG and De Mets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.

Lederman L. Fastric Cancer: local and global burden. Supplement: the current and future management of gastric cancer. Am J Manag Care. June 29, 2017:2-5.

Lee HH, Hur H, Kim SH, Park AR, Kim W, Jeon HM. Outcomes of Modified FOLFOX-6 as First Line Treatment in Patients with Advanced Gastric Cancer in a Single Institution; Retrospective Analysis. Cancer Res Treat. 2010;42(1):18–23.

Lee JH, Kim KS, Kim TJ, Hong SP, Song SY, Chung JB, et al. Immunohistochemical analysis of claudin expression in pancreatic cystic tumors. Oncol Rep. 2011;25:971-78.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines): Gastric cancer. National Comprehensive Cancer Network (NCCN). 2017; version 1.2017.

Niimi T, Nagashima K, Ward JM, Minoo P, Zimonjic DB, Popescu NC, et al. claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. Mol Cell Biol. 2001;21(21):7380-90.

Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29:3968-76.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol.1982;5(6):649-55.

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol.1998;16(1):139-44.

Pasini F, Fraccon AP, De Manzoni G. The role of chemotherapy in metastatic gastric cancer. Cancer Res. 2011;31:3543-54.

Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381:400-12.

Sahin U, Koslowski M, Dhaene K, Usener D, Brandenburg G, Seitz G, et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. Clin Cancer Res. 2008;14(23):7624-34.

Sanada Y, Hirose Y, Osada S, Tanaka Y, Takahashi T, Yamaguchi K, et al. Immunohistochemical study of claudin 18 involvement in intestinal differentiation during the progression of intraductal papillary mucinous neoplasm. Anticancer Res. 2010;30:2995-3003.

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15(Suppl 4):241-43.

Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Wotherspoon A, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomized, open-label phase 3 trial. Lancet Oncol. 2013;14(6)481-89.

Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15:1224-35.

12 APPENDICES

12.1 Ethical, Regulatory, and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, all applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Competent Authorities (CA)

GCP requires that the clinical protocol, any protocol amendments, the IB, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IRB/IEC approval before to implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

1. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
2. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
3. Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, CA approval or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new informed consent must also be forwarded to the sponsor.

12.1.4 Informed Consent of Subjects

12.1.4.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative (if applicable), and answer all questions regarding this study.

An optional partial screening ICF may be available to allow central testing of tissue for CLDN18.2 and HER2 only.

Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed (***UNIQUE TO JAPAN REGION****:* place a personal seal) and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed (***UNIQUE TO JAPAN REGION:*** or sealed) ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

12.1.4.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF (***UNIQUE TO JAPAN REGION:*** place a personal seal). A copy of the signed (***UNIQUE TO JAPAN REGION:*** or sealed) ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

12.1.5 Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electric devices) as part of regulated clinical study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol related assessments, AE tracking, and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information (if applicable). All printed records must be kept in the subject file and available for archive.

12.1.6 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, eCRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

12.1.7 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless otherwise the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then sponsor shall serve as the controller of such data, as defined by the European Union (EU) Data Protection Directive, and Investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If sponsor is not based in the EEA, sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

12.1.8 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

12.1.9 Insurance of Subjects and Others (UNIQUE TO JAPAN REGION/STUDIES ENROLLING SUBJECTS IN EU)

If a subject suffers any study-related injury, the sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.

2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the investigator's file.

12.1.10 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report, which forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

12.2 Procedure for Clinical Study Quality Control

12.2.1 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, including source documents when they are requested by the sponsor monitors and auditors, the IRB/IEC or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

Remote source data review will be used when needed. It will focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data will be monitored simultaneously, provided this does not result in a need to access additional documents and therefore increase the burden for site staff. The sponsor will determine the extent and nature of remote source data review that is needed for any exceptional situations and will carefully weigh it against the extra burden that introduction of any alternative measures would put on site staff and facilities.

12.2.3 Data Management

Data Management will be coordinated by the Data Science of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary, respectively.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

12.3 Contraception Requirements

WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Schedule of Assessments [Table 1].

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
3. Postmenopausal

Documentation of any of these categories can come from the site personnel's review of the female subject's medical records, medical examination, or medical history interview.

A postmenopausal state is defined as at least 12 months after last regular menstrual bleeding without an alternative medical cause.

1. In case the last regular menstrual bleeding cannot be clearly determined, confirmation with repeated FSH measurements of at least > 40 IU/L (or higher per local institutional guidelines), is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required at the time of informed consent and until the end of relevant systemic exposure, defined as 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs[a].

Highly Effective Contraceptive Methods (Failure rate of <1% per year when used consistently and correctly)[b]

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

1. oral
2. intravaginal

3. transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation

1. oral
2. injectable
3. implantable

Hormonal methods of contraception containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)

1. intrauterine device (IUD)
2. bilateral tubal occlusion

Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*

Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected.)*

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during treatment and until the end of relevant systemic exposure defined as 6 months after final drug administration.

1. Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
2. Male participants are required to use a condom during treatment and until end of relevant systemic exposure defined as 6 months after final drug administration.
3. Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 6 months after final drug administration.

12.4 Concomitant Medication Restrictions or Requirements

Prohibited Concomitant Treatment

The following are strictly prohibited:

- Sorivudine or analogs (during 5-FU treatment)
- Concurrent non-steroid systemic immunosuppressive agents (for systemic corticosteroids, see cautionary concomitant treatment below).
- Live vaccines should be avoided during the treatment period in which subject is receiving oxaliplatin or 5-FU and up to 6 months after final oxaliplatin or 5-FU dose. In cases where a live vaccine is needed for COVID-19 prevention and allowed per local regulations, please contact the Medical Monitor for discussion.
- Other systemic chemotherapy, immunotherapy, radiotherapy, herbal medications or other treatments intended for antitumor activity.
    - Palliative radiotherapy for peripheral bone metastases is allowed.
    - For gastric bleeding, palliative radiotherapy is prohibited, but esophagogastroduodenoscopy with epinephrine injection is allowed.
- Investigational products or therapy other than zolbetuximab.

Cautionary Concomitant Treatment

Considerations should be given to avoid or minimize the use of the following concomitant medications, if possible, during zolbetuximab/placebo treatment:

- Systemic corticosteroids, because of their impact on the potential efficacy of zolbetuximab is not known.
    - Systemic corticosteroids should be avoided or minimized while subject is on study treatment unless required for management of an emergent medical condition (e.g., severe nausea/vomiting or HSR).
    - For a subject's first dose of zolbetuximab/placebo, it is recommended that the prophylactic use of corticosteroids be avoided.
    - Inhaled, intranasal, ophthalmic, otic and topically applied steroids are allowed.
    - Subjects are allowed to use a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg/day of hydrocortisone or up to 10 mg/day of prednisone), receive a single dose of systemic corticosteroids or receive systemic corticosteroids as pre-medication for radiologic imaging contrast use.
- Administer 5-HT3 blockers with caution in subjects who have or may develop QTc prolongation.
- NSAIDs because of the potential to cause gastric ulcers and covert bleeding.
    - In such cases where NSAID use is necessary, the use of NSAIDs with lower gastric ulcerogenic potential is preferred and concomitant gastric protection with proton pump inhibitors is recommended.

The following should be avoided or used with caution during 5-FU treatment and appropriate monitoring should be conducted:

- CYP2C9 substrates
- Metronidazole and cimetidine
- Anti-epileptic medications (e.g., phenobarbital, phenytoin and primidone)

The following should be avoided or used with caution during oxaliplatin treatment and appropriate monitoring should be conducted:

- Medications known to prolong the QT or QTc interval (refer to https://www.crediblemeds.org for a list of these medications)

12.5 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × ULN (to > 5 x ULN in subjects with liver metastases) or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase [ALP] and total bilirubin). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN (in subjects without liver metastases), > 5 x ULN (in subjects with liver metastases)	or	> 2 x ULN
Severe*	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases).
- ALT or AST > 3 × ULN and International Normalized Ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site staff is to complete the LA-CRF. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study treatment has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as a SAE. The sponsor

should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study treatment are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" in the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic subjects and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, is to be entered in the (e)CRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease, presence of liver metastases or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and (total bilirubin > 2 × ULN in subjects with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

*Hy's Law Definition—The two "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 X and greater transaminase elevations over the upper limit of normal (2 X elevations are too common in treated and untreated subjects to be discriminating).
2. Cases of increased bilirubin (to at least 2X ULN) in people with concurrent transaminase elevation to at least 3 X ULN (but it is almost invariably higher) and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome. [Temple, 2006]

FDA Guidance for Industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3 x ULN, 1 or more also show elevation of serum total bilirubin to > 2 x ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and total bilirubin, such as viral hepatitis A, B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

References

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3.

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.6 Common Serious Adverse Events

The following is a list of SAEs that the sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in [Section 5.5.2 Definition of Serious Adverse Events]. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs". The investigator is required to follow the requirements detailed in [Section 5.5.5 Reporting of Serious Adverse Events].

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicates they occur more frequently with study treatment, an expedited IND safety report may be submitted to the FDA.

AEs most likely related to Gastric or GEJ adenocarcinoma:

- Gastric reflux
- Abdominal pain
- Abdominal distention
- Dysphagia
- Loss of appetite

12.7 Pharmacogenomic Analysis with Banked Samples (Optional)

INTRODUCTION

Pharmacogenomic (PGx) research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug. Samples for PGx are optional and will only be collected as allowed per local policy.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study, if applicable per local policy. As part of this sub-study, subjects must provide written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide 1 approximately 4–6 mL tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped to a designated banking CRO as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis if evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hard-lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the PGx analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.8 Eastern Cooperative Oncology Group Performance Status Scale

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all 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

Reference: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

12.9 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments/Table 1 unless the site PI determines the need to implement the alternate measures. The PI should notify Astellas and/or their CRA when these alternate measures are needed.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in Table 1 due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent which explicitly informs them of the nature of, and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the PI or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible
- Site facilities have been closed for clinical study conduct
- Site has been restricted to treating patients with conditions outside of the scope of the study
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel
- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel

- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel
- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety

Adherence to the original protocol as reflected in the Schedule of Assessment Table 1 is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 10] below are only permissible in the event of a crisis, and after discussing the need with the Astellas Medical Monitor to implement the alternate measures. This is to allow for continuity of receiving investigational medicinal product (IMP) and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

Table 10 Alternate Schedule of Assessments in Response to a Crisis

Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
Treatments														
Antiemetic Pretreatment[4]	Can be administered at home per SOC	X	X	X	X	X	X	X	X					
Zolbetuximab/Placebo[5]	Window of -2 days acceptable; as long as C1D1 is conducted at the study site, C1D22 can be skipped	X		X		X		X						
Post-Infusion Observation Period[6]	Decrease of initial observation period to 1 hour and subsequent observation period to 30 min is acceptable if there are no AEs of ≥ grade 2	X	X	X	X	X	X	X	X					

Table continued on next page

Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
mFOLFOX6[7,8]	No change in Day 1 administration; Day 15 and Day 29 visits can be conducted locally per SOC by oncology qualified personnel if zolbetuximab/placebo dosing visits continue at the investigative site as planned on at least Day 1 of each cycle and dosing records can be obtained from the treating facility	X	X		X									
5FU + Folinic Acid[8]	No change in Day 1 administration; Day 15 and Day 29 visits can be conducted locally per SOC by oncology qualified personnel if zolbetuximab/placebo dosing visits continue at the investigative site as planned on at least Day 1 of each cycle and dosing records can be obtained from the treating facility					X	X		X					
Safety Assessments														
Physical Examination[9]	Protocol allows for targeted exam after C1D1. If physical exam is not able to be completed after C1D1 that is acceptable.	X		X		X		X						

Table continued on next page

Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
Weight[9]	If there are no associated active AEs, acceptable if weight is not done at Study Treatment Discontinuation Visit and 30-day Safety Follow-up Visit.	X		X		X		X						
Vital Signs[10]	If Day 15 and Day 29 dosing is administered at local facility, SOC can be applied; if there are no associated active AEs missed assessments at Study Treatment Discontinuation Visit and 30-day Safety Follow-up Visit acceptable; Vital Sign frequency during post observation period can be decreased.	X	X	X	X	X		X						
ECOG Performance Status[9]	Not required at Study Treatment Discontinuation visit; may be assessed and captured via phone contact.	X		X		X		X						

Table continued on next page

Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
12-lead ECG [11]	ECGs allowed up to 4 days prior to treatment visits after C1D1 and can be done locally but must be available for review prior to treatment; if dosing visits on Day 15 or Day 29 are conducted at local facility, SOC ECG monitoring would be acceptable; Study Treatment Discontinuation Visit and 30-Day Safety Follow Up Visit required only if clinically indicated	X	X	If clinically indicated	X	If clinically indicated								

Table continued on next page

Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
Image Assessment[12]	At select visits, efficacy assessment using radiological examinations are required. Imaging assessment can be done locally but must be available for submission to central imaging vendor. Independent central reading of locally obtained scans can be facilitated by sharing of Image Acquisition Guidelines from study site to local site if applicable. Investigational site will be requested to re-read the scan performed at local site. If investigational site read is not an option, the investigator should discuss the case with the local institution radiologist. The local site imaging report is required.	Every 9 weeks ± 7 days from C1D1 for the first 54 weeks and then every 12 weeks ± 7 days thereafter												
Subject Contact[22]	Long Term Survival and Safety follow-up visits can be conducted phone.										X	X	X	X
Laboratory Tests														
Biochemistry[13]	Sample may be collected up to 4 days prior to treatment visit; collection of samples at local facility acceptable if results can be made available to investigative site.	X	X	X	X	X	X	X	X	X	X			

Table continued on next page

Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1[5]**	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
TSH and Free T4[13]	If this testing is unable to be performed, this is acceptable.	If clinically indicated								X				
Hematology[13]	Sample may be collected up to 4 days prior to treatment visit; collection of samples at local facility acceptable if results can be made available to investigative site.	X	X	X	X	X	X	X	X	X	X			
Coagulation Parameters (PT, PTT and INR)[14]	None as protocol allows SOC if clinically indicated. If the subject is not on a concomitant medication that affects these parameters, acceptable if these are not done.	If clinically indicated												
Urinalysis [13]	Sample may be collected up to 4 days prior to treatment visit; collection at local facility also allowed.	X		X		X		X		X	X			
Serum Pregnancy Test[15]	Collection at local facility also allowed.	If clinically indicated and/or per local requirements												
Urine Pregnancy Test [16]	Collection at local facility also allowed if results can be made available to investigative site. Sample may be collected up to 4 days prior to treatment visit C1D1.	X		X		X		X		X	X			

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Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
Sampling														
Pharmacokinetic **zolbetuximab** [23]	Samples at predose/EOI will be collected if subject receives treatment at investigative site. If central lab cannot receive samples, samples can be stored at sites in -70°C freezer until shipping is accepted again. Follow-up samples will be collected if subject visits the investigative site.	X		X		X					X	X		
Anti-Drug Antibodies (ADA for Immunogenicity) [24]	If subject is dosed or visits investigative site, ADA samples should be collected. Samples cannot be collected at local facility. Sample collection prioritized if clinically indicated. If central lab cannot receive samples, samples can be stored at sites in -70°C freezer until shipping is accepted again.	X		X		X					X	X		

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Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1**[5]	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
Genetic Immune Polymorphisms (Whole Blood)[25]	In general, biomarker samples are collected on zolbetuximab treatment days and do not require a unique visit to the study site. If samples can be collected but central labs cannot receive samples, samples can be stored at sites until shipping is accepted again.	X												
Exploratory Biomarkers (Serum)[26]	In general, biomarker samples are collected on zolbetuximab treatment days and do not require a unique visit to the study site. If samples can be collected but central labs cannot receive samples, samples can be stored at sites until shipping is accepted again.	X		X						X				
Exploratory Biomarkers (Plasma)[26]	In general, biomarker samples are collected on zolbetuximab treatment days and do not require a unique visit to the study site. If samples can be collected but central labs cannot receive samples, samples can be stored at sites until shipping is accepted again.	X		X						X				

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Critical Assessment	Alternate Approach(es)	Critical Timepoint†								Follow-up Period				
		Cycles 1 to 4				Cycle 5+				Study Treatment Discontinuation Visit [18]	30-Day Safety Follow-up Visit(s) [19]	90-Day Safety Follow-up Visit(s) [20]	Post Treatment Follow-up Period [21]	Long Term and Survival Follow-up Periods [22]
Cycle Day		**1[5]**	**15**	**22**	**29**	**1**	**15**	**22**	**29**					
Whole Blood Sample for PGx (optional)[27]	In general, biomarker samples are collected on zolbetuximab treatment days and do not require a unique visit to the study site. If samples can be collected but central labs cannot receive samples, samples can be stored at sites until shipping is accepted again.	X												
Post-Progression Tumor Sample (optional)[28]	In general, biomarker samples are collected on zolbetuximab treatment days and do not require a unique visit to the study site. If samples can be collected but central labs cannot receive samples, samples can be stored at sites until shipping is accepted again.									X				
Concomitant Medication[29]	Remote/Virtual Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X	X	X	X	X		
AEs/SAEs[30]	Remote/Virtual Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X	X	X	X	X		

Footnotes appear on next page

ADA: anti-drug antibodies; AE: adverse event; βhCG: beta human chorionic gonadotropin; C1D1: Cycle 1 Day 1; CLDN: Claudin; CT: computerized tomography; ECG: electrocardiogram; eCOA: electronic Clinical Outcomes Assessment; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; EOI: end of infusion; FFPE: formalin fixed paraffin embedded; HER2: human epidermal growth factor receptor 2; HRQoL: health-related quality of life; HRU: Health Resource Utilization; ICF: informed consent form: INR: international normalized ratio; IRC: independent review committee; IRR: infusion-related reaction; IV: intravenous; mFOLFOX6: 5-fluorouracil, folinic acid and oxaliplatin; MRI: magnetic resonance imaging; OS: overall survival; PD: progressive disease; PFS: progression free survival; PFS2: progressive disease following 2nd line therapy; PGx: pharmacogenomics; PT: prothrombin time; PTT: partial thromboplastin time; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid stimulating hormone

†In case subjects are unable to be evaluated in person on Day 1 of each cycle, the site will contact the subject by phone for a safety assessment at the time the next visit would be due.

*+ 6 calendar day visit window does not apply to C1D1.

1. Screening: The Screening period is 45 days from full main ICF signature. Re-testing of lab values is allowed within the 45-day screening period. Re-screening outside of the 45-day window under a new subject number may be allowed once and upon discussion with the Medical Monitor. CT scans and MRIs conducted as part of a subject's routine clinical management (i.e., standard of care) obtained prior to signing the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the Screening period.
   - Optional Partial Screening: A partial screening ICF may be available for central testing of tissue for CLDN18.2 and HER2 only.
   - Laboratory testing:
     Eligibility can be determined based on central and/or local testing, however:
     - The most recent laboratory tests with available results must be used to confirm the subject's eligibility.
     - Central labs must be collected and submitted to the central laboratory during the Screening period.
     - If retesting of lab values is necessary to confirm eligibility, local labs can be used without requiring additional sample collection for central laboratory submission.
     - The screening labs used to determine eligibility should be collected within 14 days prior to randomization.
   - Radiologic imaging used to confirm eligibility must be conducted within 28 days prior to randomization.
2. CLDN18.2 and HER2 Testing: FFPE tumor tissue will be collected for central testing to determine CLDN18.2 and HER2 status. Archival tumor tissue from the primary tumor (gastric or GEJ) is preferred. If primary tumor tissue is not available, tumor tissue from a metastatic site (excluding bone metastasis) may be used. A minimum of 1 FFPE tumor tissue block (preferred) OR a minimum of 15 FFPE unstained slides are required, as allowed per local policy. If slides are submitted, the slides should be freshly cut from the FFPE block within the time frame described in the laboratory manual. If local HER2 results are already available from local testing, a minimum of 12 FFPE unstained slides are required to be submitted to the central lab, as allowed per local policy. If the specimen is insufficient or unavailable, a biopsy may be performed to obtain primary tumor tissue (preferred) or tumor tissue from metastatic site (excluding bone metastasis). Sponsor pre-approval is required when the sole purpose of the biopsy procedure is to assess eligibility for this study. See [Section 5.7.3 Tumor Tissue Samples].
   If the required number of slides cannot be provided, the sponsor or designee should be contacted for further guidance.
3. Randomization: After confirmation of eligibility, the blinded site user will perform the randomization IRT transaction. The unblinded pharmacist/designee will be notified by the IRT system about the randomly assigned treatment. Confirmation of Inclusion/Exclusion Criteria must be completed prior to randomization. Randomization may be performed prior to C1D1. If C1D1 cannot be performed within 5 calendar days from Randomization, please contact the Medical Monitor. Details of infusion preparation and storage requirements are defined in the Pharmacy Manual and Infusion Guidelines.

Footnotes continued on next page

4. Antiemetic Pre-treatment: Antiemetic premedication (prophylactic antiemetics) should be administered prior to each study treatment. IV antiemetic premedication should be initiated prior to treatment, or oral antiemetic premedication should be initiated at a minimum of 30 minutes prior to treatment. Antiemetic premedication should be given according to institutional standard of care, published guidelines and the respective product package insert(s). For further details, see [Section 5.1.1.2 Antimemetics].
5. Zolbetuximab/placebo will be administered as a minimum 2-hour IV infusion every 3 weeks starting on C1D1 (i.e., C1D1, C1D22, C2D1, etc.). Please refer to the Pharmacy Manual and Infusion Guidelines for more detailed information. If both zolbetuximab/placebo and mFOLFOX6 are to be administered during the same visit, zolbetuximab/placebo should be administered prior to mFOLFOX6. For further details, see [Section 5.1.1.1 Zolbetuximab/Placebo].
6. Post-Infusion Observation Period: Following the first dose of zolbetuximab/placebo in C1, the subject must be observed for 2 hours post-zolbetuximab/placebo infusion. The post-infusion observation period can be conducted during the mFOLFOX6 administration. If any ≥ grade 2 AEs are observed during infusion or during the post-infusion observation period, subsequent zolbetuximab/placebo infusion times should be extended and subjects should continue to be observed for 2 hours post zolbetuximab/placebo infusion. If the subject does not develop any ≥ grade 2 AEs, the subject should be observed for 1 hour post-infusion for their subsequent zolbetuximab/placebo infusions. The subject should be instructed to notify site personnel if they develop any AEs during this observation time period. In the event of an IRR with features of anaphylaxis (regardless of grade) or grade 3 or 4 IRR, blood, samples for cytokine/chemokine panel and serum total tryptase level (levels typically peak within 3 hours after the onset of symptoms) should be collected once the subject has stabilized for shipment to the central laboratory. See Observation Period following zolbetuximab/placebo [Section 5.4.2] for further details.
7. mFOLFOX6 will be administered every 2 weeks starting at C1D1 (i.e., C1D1, C1D15, C1D29, etc.) for 4 cycles (up to 12 treatments). A maximum of 12 doses of oxaliplatin can be administered. If both zolbetuximab/placebo and mFOLFOX6 are to be administered during the same visit, zolbetuximab/placebo should be administered prior to mFOLFOX6. See [Section 5.1.1.3 mFOLFFOX6].
8. 5-FU and Folinic Acid may continue to be administered at the discretion of the investigator after completion of 12 treatments of mFOLFOX6. If 5-FU is not continued after 12 treatments of mFOLFOX6, then day 15 and day 29 visits are not required. If both zolbetuximab/placebo and 5-FU and folinic acid are to be administered during the same visit, zolbetuximab/placebo should be administered first. See [Section 5.1.1.1 Zolbetuximab/Placebo].
9. Physical Exam: should include height (at Screening only), weight and ECOG performance status. A full physical exam is required at Screening. The physical exam only needs to be repeated on C1D1 if clinically significant changes from Screening are observed (in the opinion of the investigator). For all cycles, the physical examination, weight and ECOG performance status assessments can be completed up to 48 hours prior to zolbetuximab/placebo administration. Targeted (symptom driven) physical exams should be conducted every 3 weeks on zolbetuximab/placebo visit days. For further details, see [Section 5.4.4 Physical Examination].
10. Vital signs (pulse, blood pressure, temperature) should be taken during every visit at the following time points (see [Section 5.4.1 Vital Signs]):
    - Pre-dose at every visit
    - C1D1: Every 30 (± 10) minutes during zolbetuximab/Placebo infusion
    - If the subject did not develop any ≥ grade 2 AEs during the C1D1 zolbetuximab/placebo infusion or the Post-Infusion Observation Period, the site may do the following for subsequent zolbetuximab/placebo infusions:
        - The post-infusion observation period can be 1 hour for subsequent visits after C1D1
        - The vital signs can be assessed every 60 minutes for subsequent visits after C1D1
    - Every 60 (±10) minutes post zolbetuximab/placebo infusion during the Post-Infusion Observation Period (for 1 or 2 hours. See footnote 6)
    - Unscheduled if clinically indicated

Footnotes continued on next page

11. ECGs: ECGs will be locally read. When collected on the same day, ECG should be collected prior to pharmacokinetic samples. For further details, see [Section 5.4.5 Electrocardiogram]. A single ECG will be performed at the following time points:
    - Screening
    - Up to 48 hours prior to every oxaliplatin infusion (before any antiemetic treatment)
    - Up to 6 hours following completion of every oxaliplatin infusion
    - Zolbetuximab/placebo study treatment discontinuation visit
    - Zolbetuximab/placebo 30-day safety follow-up visit
    - If clinically indicated and/or per local requirements
12. Imaging Assessments: Radiologic imaging will be evaluated at Screening (must be conducted within 28 days prior to randomization) and every 9 weeks (± 7 days) counting from C1D1 for the first 54 weeks and then every 12 weeks (± 7 days) thereafter until subject develops radiological disease progression per RECIST 1.1 by IRC or starts other systemic anticancer treatment, whichever comes earlier. Imaging schedule should be maintained regardless of treatment delay. Imaging will include CT scans with contrast of the thorax, abdomen, and pelvis. If CT scan with contrast is medically not feasible, MRI may be used for imaging. Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease in bone or brain is suspected, respectively. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change. For randomized subjects, screening imaging should be sent to the central imaging vendor no later than submission of the first on-treatment imaging. All imaging acquired post randomization will be sent to the central imaging vendor within 7 days of scanning for the blinded independent central assessment of radiological tumor response based on RECIST 1.1. The investigator should make every effort to immediately submit radiologic assessments for IRC review when PD is suspected. See [Section 5.3 Efficacy Assessments]. Refer to Imaging Acquisition Guidelines for further detail on scan modality and contrast options.
13. Laboratory Assessments: See [Section 5.4.3 Laboratory Assessments] for list of laboratory assessments. Laboratory tests must be sent to the central laboratory for analysis unless otherwise approved by the sponsor. For screening/eligibility laboratory assessments, see footnote 1.
    - Laboratory test results (central or local) will be reviewed by the investigator prior to any study treatment. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.
    - Local laboratory results may be used for treatment decisions; however, central laboratory samples must also be drawn per protocol and sent to the central laboratory unless otherwise approved by the sponsor.
    - Central and local labs may be collected up to 48 hours prior to study treatment.
    - Holidays and weekends should be taken into account when scheduling these blood draws.
    - Additional assessments may be done centrally or locally to monitor AEs or as clinically indicated.
14. Coagulation (PT, PTT and INR): Coagulation tests should be done at Screening and during study treatment period if clinically indicated. Local or central lab results may be used to confirm eligibility. Ongoing evaluation should be continued for Subjects who are receiving therapeutic anticoagulation according to local standard of care. See [Section 5.4.3 Laboratory Assessments].
15. Serum Pregnancy Test: Serum pregnancy tests will be collected for female subjects of child bearing potential only. Serum pregnancy tests collected at Screening, during study treatment period and if clinically indicated or per local requirements. Serum pregnancy test can be completed up to 48 hours prior to zolbetuximab/placebo administration. (Note: For Screening, subjects with elevated serum βHCG and a demonstrated non-pregnant status through additional testing are eligible.) Local or central laboratory results may be used to confirm eligibility.

Footnotes continued on next page

16. Urine Pregnancy Test: for female subjects of child bearing potential only. Local urine pregnancy tests to be performed during the treatment period every 3 weeks at zolbetuximab/placebo visits and at the zolbetuximab/placebo Study Treatment Discontinuation and 30-Day Safety Follow up Visits. Urine pregnancy test can be completed up to 48 hours prior to zolbetuximab/placebo administration Additional urine pregnancy testing for up to 9 months after the final study treatment administration may be applied based on local requirements.
17. HRQoL and HRU questionnaires: eCOA questionnaires are to be completed by the subject at Screening (except HRU), on day 1 and day 22 of each cycle (or up to 48 hours) before any antiemetic or drug treatment and before the disease status is discussed with the subject using the electronic tablet device provided. When completion by the subject is not possible, the questionnaires may be administered to the subject by site personnel using the electronic tablet device. For subjects with low literacy, situations where translations are unavailable or other circumstances preventing the screening questionnaires to be completed, please contact the sponsor for further guidance.
18. Study Treatment Discontinuation Visit (End of Study Treatment): The Study Treatment Discontinuation Visits will take place ≤ 7 days following the decision to discontinue all study treatment (zolbetuximab/placebo and mFOLFOX6 (all components). If zolbetuximab/placebo and mFOLFOX6 (all components) are discontinued on a different day, subjects will have a separate Study Treatment Discontinuation Visit following each treatment's discontinuation. Laboratory tests must be sent to the central laboratory for analysis. HRQoL and HRU questionnaires are not required at mFOLFOX6 treatment discontinuation visit. A combined visit can be completed if zolbetuximab/placebo are discontinued on the same day. If necessary during a crisis, this visit can be completed remotely for safety assessments and the required laboratory samples should be collected as soon as the crisis permits.
19. 30-Day Safety Follow-up Visit: A 30-Day Safety Follow-up visit should occur 30 days after the last dose of zolbetuximab/placebo and will include the assessments as shown in the Schedule of Assessments above. A 30-Day Safety Follow-Up Visit should occur 30 days after the last dose of mFOLFOX6 (all components) and may be conducted by phone if the subject is unable to visit the site and will require only contact for AE/SAE collection. HRQoL and HRU questionnaires are not required at mFOLFOX6 30-day safety follow up visit. A combined visit can be completed if zolbetuximab/placebo and all components of mFOLFOX6 are discontinued on the same day and HRQoL and HRU questionnaires should be completed for a combined visit. If necessary during a crisis, this visit can be completed remotely for safety assessments and the required laboratory samples should be collected as soon as the crisis permits.
20. 90-Day Safety Follow-up Visits: A 90-Day Safety Follow-up visit should occur 90 days after the last dose of zolbetuximab/placebo will include the assessments as shown in the Schedule of Assessments above. A 90-Day Safety Follow-Up Visit should occur 90 days after the last dose of mFOLFOX6 (all components) and may be conducted by phone if the subject is unable to visit the site and will require only contact for AE/SAE collection. HRQoL and HRU questionnaires are not required at mFOLFOX6 90-day safety follow up visit. A combined visit can be completed if zolbetuximab/placebo and all components of mFOLFOX6 are discontinued on the same day and HRQoL and HRU questionnaires should be completed for a combined visit.
21. Post-Treatment Follow-up: if a subject discontinues all study treatments (zolbetuximab/placebo and all components of mFOLFOX6) prior to IRC confirmed radiological disease progression, the subject will enter the Post-Treatment Follow-up Period and continue to undergo imaging assessments every 9 weeks (or every 12 weeks if subject has been on study over 54 weeks) until radiologic disease progression (i.e., PFS) or the subject starts subsequent anticancer treatment, whichever occurs earlier. If study treatment (zolbetuximab/placebo and all components of mFOLFOX6) is discontinued due to PD, the subject will enter the Long Term and Survival Follow-up Period.
22. Long Term and Survival Follow-up Period: Following disease progression on 1st line treatment or start of subsequent anticancer treatment, subjects will be followed in the Long-Term and Survival Follow-up Period per institutional guidelines, but not less frequently than every 12 weeks. Radiologic imaging will be done per standard of care and read locally. Survival Follow-up Period will continue until death (from any cause). All post-progression details including subsequent anticancer treatment and date and site of progression will be recorded on the eCRF. Subject contact by phone or other remote methods is sufficient during Long Team and Survival Follow-up.

Footnotes continued on next page

23. Pharmacokinetic (Serum) for zolbetuximab/placebo samples will be taken at the below timepoints and sent to the central laboratory. The date and time of each blood sample collection will be recorded to the nearest minute.
    - Cycle 1 Day 1: End of zolbetuximab/placebo infusion
    - Cycle 1 Day 22: Predose
    - Cycle 2 Day 1: End of zolbetuximab/placebo infusion
    - Pre-dose on Day 1 of Cycles 3, 5, 7 and 9
    - Zolbetuximab/placebo 30-Day Safety Follow-up visit
    - Zolbetuximab/placebo 90-Day Follow-up visit
    - Unscheduled pharmacokinetic blood samples may be taken at any time during the study to evaluate drug exposure following a safety event

    Pharmacokinetic Sampling Window:
    - Predose: within 60 minutes prior to dosing
    - End of Infusion: within 10 minutes after the end of the infusion
24. Anti-Drug Antibodies (ADA): Blood samples (Serum) for ADA will be taken at the below timepoints and sent to the central laboratory.
    - Cycle 1 Day 1: Predose
    - Cycle 1 Day 22: Predose
    - Pre-dose on Day 1 of Cycle 3, 5, 7 and 9
    - Zolbetuximab/placebo 30-Day Safety Follow-up visit
    - Zolbetuximab/placebo 90-Day Follow-up visit

    ADA Sampling Window: Predose: within 60 minutes prior to dosing
25. Genetic Immune Polymorphism: To be collected per local policy. Whole blood sample taken at C1D1 will be sent to the central laboratory. Samples may be collected up to 48 hours prior to study treatment.
26. Exploratory Biomarker (Serum and Plasma): To be collected per local policy. Samples should be taken at the below timepoints and sent to the central laboratory:
    - Cycle 1 Day 1: Predose
    - Cycle 1 Day 22: Predose
    - Cycle 2 Day 1: Predose
    - Cycle 2 Day 22: Predose
    - Cycle 3 Day 1: Predose
    - Cycle 3 Day 22: Predose
    - Cycle 4 Day 22: Predose
    - Zolbetuximab/placebo Study Treatment Discontinuation Visit

    Exploratory Biomarker samples may be collected up to 48 hours prior to study treatment
27. Optional PGx: for subjects who signed a separate ICF, an optional whole blood sample for PGx for exploratory biomarker analysis may be collected up to 48 hours prior to first study drug administration at C1D1. Sample collection is optional and only collected as allowed per local policy.

Footnotes continued on next page

28. Optional Post-Progression Tumor Sample: for subjects who signed a separate ICF, an optional post-progression tumor sample for exploratory biomarker analysis may be collected following IRC confirmation of disease progression and prior to initiation of subsequent anticancer therapy. Sample collection is optional and only collected as allowed per local policy.
29. Concomitant medications: Concomitant medications will be collected from the time of full main informed consent through 90 days following the last dose of study treatment.
30. AEs/SAEs: AEs/SAEs (regardless of causality) will be collected from the time of full main informed consent through 90 days following the last dose of study treatment. See [Section 5.5.5 Reporting of Serious Adverse Event].

IMP SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of IMP supply to the participants:

- Increase stock of IMP on site to reduce number of shipments required, if site space will allow, as cold storage space is needed.

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 4

Protocol Amendment Summary of Changes

Protocol 8951-CL-0301 A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

Amendment 4 [Substantial] 18 Oct 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

Reduction in the number of PFS events required for primary analysis as well as addition of key secondary endpoints for health-related quality of life questionnaires**Summary of Changes**

Table 1 Substantial Changes

Section Number	Description of Change	Brief Rationale
IV, 2.1.2, 2.3.2, 5.7.6.1, 5.7.6.2, 7.4.2.2	Addition of health economics and outcomes research (HEOR) related key secondary endpoints, including physical function, Pain, and Global Health Score.	A key secondary endpoint for QOL measures has been added after FDA interaction in order to more specifically address the effect of zolbetuximab in gastric/GEJ cancer, which impacts the risk/benefit assessment.
IV, 2.2.1, 7.1, 7.4.1.1	The number of PFS events required for the interim analysis of overall survival is reduced from 368 to 300.	The number of required PFS events has been adjusted based on the enrollment and event accrual rates to maintain the timing of Primary Analysis with adequate power which is > 93%.
IV, 5.1.5, 12.4	Clarify that a subject receiving oxaliplatin should not receive live vaccines.	Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents may result in serious or fatal infections.
Table continued on next page		

Section Number	Description of Change	Brief Rationale
IV, 7.2.2, 7.3, 7.4, 7.4.1.2, 7.4.2.1	The Per Protocol Set (PPS) has been removed from the protocol.	The PPS is defined as the subjects who do not meet predetermined study entry and treatment criteria as well as those with lack of imaging assessment. The data from subjects meeting these criteria are unlikely to allow adequate assessment of potential impact on treatment benefit, possibly resulting in risk of bias. Therefore, the robustness of treatment benefit in Primary Endpoint will instead be assessed through sensitivity analyses applying different censoring rules.

Table 2 Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
II	Contact details for the clinical research contact and global clinical research contact are updated.	Contact details of sponsor personnel are updated based on changes to study personnel.
IV	Correct planned study period to end 2Q2023	To reflect the length of the planned study period
IV, V (Table 1 [footnote 1]), 2.2.1, 12.9 (Table 10 [footnote 1])	Specify that CT scans and MRIs conducted as a part of a subject's routine clinical management obtained prior to signing the informed consent form may be utilized for screening or baseline purposes. ECGs removed from the change in text.	Additional instructions are provided for clarity.
IV, V (Table 1 [footnote 4]), 5.1.1.2, 12.9 (Table 10 [footnote 4])	Text revised to clarify prophylactic antiemetic management.	To clarify the timing of oral and IV antiemetics.
Table continued on next page		

Section Number	Description of Change	Brief Rationale
IV, V (Table 1 [footnotes 15 and16]), 3.2 (inclusion criteria #4 and #6), 5.5.9.1, 12.3, 12.9 (Table 10 [footnotes 15 and 16])	Contraceptive guidance is updated to clarify that requirements are applicable for 9 months after the final administration of oxaliplatin and 6 months after the final administration of all other study drugs.	To align with the FDA label for oxaliplatin use in ensuring adequate contraception and pregnancy testing
IV, 3.2 (inclusion criterion #17), 5.4.3	This inclusion criterion is updated to clarify that when multiple blood draws are done, the most recent sample collection with available data should be used for determination of eligibility.	This revision is made for clarification.
IV, 3.3 (exclusion criterion #1)	Subjects are not prohibited from participation if they received prior immunotherapy or other systemic anticancer therapies as long as it was completed at least 6 months prior to randomization.	Clarified the types of immunological therapies that are not prohibited.
V (Table 1 [general footnote]), 12.9 (Table 10 [general footnote])	Footnote added to clarify that in case subjects are unable to be evaluated in person on day 1 of each cycle, the site will contact the subject by phone for a safety assessment at the time the next visit would be due.	This revision is made for clarification.
V (Table 1 [footnotes 9, 15, and 16]), 5.4.4, 12.9 (Table 10 [footnote 9])	Clarify that the urine and serum pregnancy tests, physical examination, weight and ECOG performance status assessments can be completed up to 48 hours prior to zolbetuximab/placebo administration.	To provide a window for pre-treatment testing to decrease subject burden and align with standard subject flow for pre-treatment testing.

Table continued on next page

Section Number	Description of Change	Brief Rationale
V (Table 1 [footnote 10]), 12.9 (Table 10 [footnote 10])	The vital sign observation period for subsequent zolbetuximab/placebo infusions is updated to include a reduction of observation time from every 30 minutes to every 60 minutes and a reduction of intervals for assessing vital signs in some situations.	This revision is made for clarification and to decrease the burden on subjects.
1, 2.2.2	Text is added to clarify that the standard of care when discussing fluoropyrimidine with platinum-based combination chemotherapy regimens is the standard of care cytotoxic chemotherapy regimen.	This revision is made for clarification.
1.1	Remove paragraph referencing normal epithelia.	Based on a further interpretation of the data, there was insufficient evidence to support this statement.
5.1.2.4	Text added to indicate that dose re-escalation of 5-FU is permitted after the subject has completed 4 cycles or 12 doses of mFOLFOX6 if the investigator chooses to continue 5-FU.	To clarify that once oxaliplatin therapy is completed and if capecitabine is continued the dose may be increased as a monotherapy.
5.1.2.8 (Table 8)	Dose modifications for oxaliplatin related to neurotoxicity is updated to describe that for Grade 3 neurotoxicity > 7 days/persistent between treatments, discuss oxaliplatin discontinuation with Medical Monitor.	To allow discussion with Medical Monitor to determine if the subject's oxaliplatin treatment should be discontinued or continued.
5.4.5	Text added to clarify that clinically significant ECG findings should be recorded as an AE.	Clarification of language as not all changes from baseline are an AE.
5.4.6	Section added to clarify that the ECOG Scale is used to assess performance status.	This revision is made for clarification.
Table continued on next page		

Section Number	Description of Change	Brief Rationale
5.5.2.1	Always Serious Adverse Events are now refered to as Important Medical Events and if an AE occurs that the sponsor determines to be an Important Medical Event, additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested.	Astellas has changed from "Always Serious Adverse Events" categorization to "Important Medical Events" to align with internal processes for medically important events.
6.3	Text is updated to clarify procedures if the study is prematurely terminated or suspended.	This revision is made for clarification.
7.8	Text is added to clarify that the analysis for the eCOA endpoints will be performed as the final analysis once OS is significant either at the interim OR or at final OS anlaysis; hence, there is no interim analysis planned for eCOA endpoints.	This revision is made for clarification.
8.1.1, 8.1.1.1	Text is added to provide details for the investigator's role in maintaining accurate source data.	Investigator's responsibilities are clarified.
8.2	Text updated to remove major protocol deviation criteria but note that major protocol deviations will be summarized at the end of the study.	This change is made to help clarify site and sponsor protocol deviation reporting requirements.
12.2.2	Text is added to describe how remote source data review will be used when needed.	This revision is made to address a process change related to source document review requirements.
12.9 (Table 10 [general footnotes])	Footnote added to clarify that: • additional non-protocol-specific testing may be required per local regulations, and • local and/or regional protocols or precautions for COVID-19 management should be followed as applicable	This revision is made for clarification.
Table continued on next page		

Section Number	Description of Change	Brief Rationale
Throughout	Minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.	To provide clarifications to the protocol and to ensure complete understanding of study procedures.

14 COORDINATING INVESTIGATOR'S SIGNATURE

A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

ISN/Protocol 8951-CL-0301

Version 5.0 Incorporating Substantial Amendment 4

18 Oct 2021

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: _____ _____

<Insert name, department/affiliation, name of institution> Date (DD Mmm YYYY)

Printed Name: _____

Address: _____

_____

15 SPONSOR'S SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document)

PPD	Oncology Development Medical Science
PPD	Biostatistics