

## CLINICAL RESEARCH PROTOCOL

**Study Title:** A Dose Escalation, Expansion Study of Vofatamab (B-701) Alone, Plus Docetaxel, or Versus Docetaxel in Subjects with Locally Advanced or Metastatic Urothelial Cell Carcinoma who have Relapsed After, or are Refractory to Standard Therapy

**Protocol Number:** FIERCE-21 (B-701-U21)

**Investigational Product:** Vofatamab (B-701) (anti-FGFR3 human monoclonal antibody)

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**Indication:** Treatment of Relapsed or Refractory Urothelial Cell Carcinoma

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## PROTOCOL SYNOPSIS

<b>Title of Study:</b>	A Dose Escalation, Expansion Study of Vofatamab (B-701) Alone, Plus Docetaxel, or Versus Docetaxel in Subjects with Locally Advanced or Metastatic Urothelial Cell Carcinoma who have Relapsed After, or are Refractory to Standard Therapy
<b>Protocol Number:</b>	FIERCE-21 (B-701-U21)
<b>Location:</b>	United States (US), European Union (EU), and Asia
<b>Study Centers:</b>	Approximately 50 to 100 sites will participate in this study.
<b>Study Period:</b>	Subjects will participate in the study for approximately 36 months, including a 28-day screening period, 21-day cycles of treatment, and telephone follow-up to monitor survival.
<b>Phase of Development:</b>	1/2(b)
<b>Study Rationale:</b> <p>Vofatamab (formerly referred to as B-701 and MFGR1877S) is a novel monoclonal antibody specific for fibroblast growth factor receptor 3 (FGFR3) that is being developed to target FGFR3-positive tumors. Studies have shown that the majority of subjects with urothelial cell carcinoma (UCC) overexpress FGFR3 on the tumor cell surface. Preclinical studies have also shown that vofatamab suppresses FGFR3-mediated cell proliferation and exerts strong anti-tumor activity in mouse xenograft models of bladder cancer. Furthermore, the combination regimen of vofatamab plus a taxane showed better anti-tumor activity than either agent alone. Potential signals of clinical efficacy following treatment with vofatamab were also observed in a Phase 1 study in subjects with advanced solid tumors, including UCC.</p>	
<b>Study Objectives:</b> <u>Phase 1b (Cohort 1)</u> <ul style="list-style-type: none"> <li><b>Primary Objective:</b> To determine an acceptable maximum tolerated dose (MTD) of vofatamab plus docetaxel in subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy.</li> </ul> <u>Phase 2 (Cohorts 2 and 3)</u> <ul style="list-style-type: none"> <li><b>Primary Objective:</b> To evaluate the initial safety and efficacy of vofatamab in combination with docetaxel and vofatamab monotherapy in advanced UCC with FGFR3 genomic aberrations.</li> </ul>	



Phase 2b Monotherapy Expansion and Randomized Phases:

Phase 2b Monotherapy Expansion Phase

- **Primary Objective:** To evaluate the efficacy of vofatamab in the treatment of subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to, at least one prior line of chemotherapy, as measured by progression-free survival (PFS).
- **Secondary Objectives:**
  - To evaluate overall survival (OS) of vofatamab in the treatment of subjects with UCC.
  - To evaluate the efficacy of vofatamab in the treatment of subjects with UCC as measured by objective response rate (ORR), disease control rate (DCR), duration of objective response (DOR), time to response (TTR), and quality of life (QOL).
  - To evaluate the safety and tolerability of vofatamab in the treatment of subjects with UCC as measured by anti-vofatamab antibodies (ATA), adverse events (AEs), physical examination, laboratory, and other clinically relevant results.
- **Exploratory Objectives:**
  - To evaluate the pharmacokinetics (PK) of vofatamab in advanced UCC

Phase 2b Randomized Phase

- **Primary Objective:** To evaluate the efficacy of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy which has not included a taxane, as measured by progression-free survival (PFS).
- **Secondary Objectives:**
  - To evaluate overall survival (OS) of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with UCC.
  - To evaluate the efficacy of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with UCC as measured by objective response rate (ORR), disease control rate (DCR), duration of objective response (DOR), time to response (TTR), and quality of life (QOL).
  - To evaluate the safety and tolerability of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with UCC as measured by anti-vofatamab antibodies (ATA), adverse events (AEs), physical examination, laboratory, and other clinically relevant results.

- **Exploratory Objectives:**

- To study the association between the level of FGFR3 expression, the presence of FGFR3 mutations or fusions, as well as other potential biomarkers (e.g., genetic alterations in other cancer-related genes), in primary tumors or metastases, with efficacy and/or adverse event (AE) outcomes.
- To evaluate the pharmacokinetics (PK) of vofatamab monotherapy and vofatamab in combination with docetaxel in advanced UCC.

**Study Design and Methodology:**

This is a Phase 1/2(b), sequential, dose escalation, open-label, randomized expansion, multicenter, efficacy and safety study of vofatamab alone or in combination with docetaxel, or versus docetaxel in subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy. This study is divided into 3 phases: Phase 1b (Cohort 1), Phase 2 (Cohorts 2 and 3), and Phase 2b (Monotherapy Expansion Phase and Randomized Phase).

**Phase 1b:**

The clinical trial will commence with Phase 1b, which consists of Cohort 1 as follows:

- Cohort 1: Approximately 20 subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy which has not included a taxane. All subjects in this cohort will receive both vofatamab plus docetaxel.

**Cohort 1 of Phase 1b:**

Cohort 1 of Phase 1b of the study will utilize the following 3 + 3 design:

Initially, one subject will be enrolled in Cohort 1. On Day 1 of Cycle 1, the initial subject in this cohort will be treated with a combination regimen consisting of an intravenous (IV) infusion of docetaxel (75 mg/m<sup>2</sup>) followed by an IV infusion of vofatamab (25 mg/kg). On Day 8 of Cycle 1, the subject will be treated with an IV infusion of vofatamab (25 mg/kg) alone. If the subject experiences a dose limiting toxicity (DLT) during the DLT observation period (defined as the first 21-day cycle), then additional subjects will be enrolled at the same dose until 6 subjects are enrolled or until  $\geq 2$  subjects have experienced DLTs. If no DLT is observed through Day 21, an additional 2 subjects will be treated, on different days, with the same regimen. If a DLT is observed in 1 of the 3 subjects during the DLT observation period, then additional subjects will be enrolled until at least 6 subjects are enrolled or until  $\geq 2$  subjects have experienced DLT (i.e., with docetaxel 75 mg/m<sup>2</sup> and vofatamab 25 mg/kg). If 0 of 3 subjects or  $\leq 1$  of 6 subjects experience a DLT, additional subjects will be enrolled at that dose so that a total of 20 subjects will be treated in Cohort 1. If at any time  $\geq 2$  of 6 subjects experience a DLT, the dosing regimen will be modified by either reducing the dose of vofatamab to 20 mg/kg and/or reducing the dose of docetaxel to 55 mg/m<sup>2</sup>. The dose modification decision will be made based upon the nature of the DLT, e.g., if it is clearly related to one or the other drug, or upon discussion with the participating

principal investigators (see [Section 5.1.2](#) for details). A new set of 3 to 6 subjects will be enrolled and treated with the modified dose of vofatamab and/or docetaxel. If at any time, a dose of vofatamab of 20 or 25 mg/kg or a dose of docetaxel of at least 55 mg/m<sup>2</sup> are deemed not tolerable (i.e.,  $\geq 2$  of 6 subjects at the same dose level who have experienced DLTs), enrollment will cease and the study will be stopped until further analysis of the combination regimen can be performed. Should a subject discontinue dosing with docetaxel at any time during the study, dosing with vofatamab will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

#### Phase 2:

Phase 2 of the study is divided in the following 2 cohorts:

- Cohort 2: Up to 20 subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy which has not included a taxane. All subjects in this cohort will receive both vofatamab plus docetaxel.
- Cohort 3: Up to 20 subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy. All subjects in this cohort will receive vofatamab only.

#### Cohort 2 of Phase 2:

Enrollment in Cohort 2 will commence after the 16<sup>th</sup> subject is enrolled in Cohort 1 of Phase 1b. On Day 1 of each 21-day cycle, subjects in Cohort 2 of Phase 2 will be treated with a combination regimen consisting of an intravenous (IV) infusion of docetaxel (75 mg/m<sup>2</sup>) followed by an IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) only will be given on approximately Day 8 of Cycle 1 only. Dosing with docetaxel and vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. Should a subject discontinue dosing with docetaxel at any time during the study, dosing with vofatamab will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

#### Cohort 3 of Phase 2:

Enrollment in Cohort 3 of Phase 2 will commence after the 16<sup>th</sup> subject is enrolled in Cohort 1 of Phase 1b. On Day 1 of each 21-day cycle, subjects in Cohort 3 of Phase 2 will receive one IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) will be given on approximately Day 8 of Cycle 1 only. Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

Phase 2b:

Phase 2b Monotherapy Expansion:

Enrollment to Monotherapy Expansion will commence once Phase 2 has completed enrollment. The Monotherapy Expansion Phase will enroll up to 80 subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy. (If a checkpoint inhibitor is not an approved or available therapy for UCC, then this criterion does not apply).

On Day 1 of each 21-day cycle, subjects in the Monotherapy Expansion Phase will receive one IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) will be given on approximately Day 8 of Cycle 1 only. Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

**Pharmacokinetic Sub-study:** up to 10 subjects at designated centers in Monotherapy Expansion who provide separate informed consent will participate in a PK Sub-study and will have intensive PK sample collection (samples obtained before and 30 minutes post-dosing) performed on Day 1 of Cycles 1, 2, 3, 5, 6, 10, and end of treatment following the initiation of vofatamab dosing. In addition, for Cycle 1, samples will be collected on Day 2 and 4, and on Day 8 before and 30 minutes post-dosing. In Cycle 5, samples will be collected on Day 2, Day 8, Day 15, and Day 21.

Phase 2b Randomized Phase:

Enrollment to the Randomized Phase will commence after a review of the safety and efficacy data observed in the Cohort 2 of Phase 2. The review will be conducted by the Sponsor and the Safety Oversight Committee (SOC) once the last subject in Cohort 2 of Phase 2 has completed at least 6 months of follow-up on study, to evaluate the potential safety and efficacy benefit of the addition of vofatamab to docetaxel chemotherapy. Subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy which has not included a taxane will be enrolled. (If a checkpoint inhibitor is not an approved or available therapy for UCC, then this criterion does not apply).

Subjects will be randomly assigned in a 2:1 ratio to receive therapy with either vofatamab plus docetaxel (Arm A, experimental arm) or placebo plus docetaxel (Arm B, control arm). Random assignment will be stratified by visceral metastasis (presence vs. absence).

Arm A (vofatamab plus docetaxel): On Day 1 of each 21-day cycle, subjects will receive one IV infusion of docetaxel followed by one IV infusion of vofatamab, using the MTD identified in Cohort 1. An additional dose of vofatamab (without docetaxel,

and at the dose identified in Cohort 1) will be given on approximately Day 8 of Cycle 1 only.

Arm B (placebo plus docetaxel): On Day 1 of each 21-day cycle, subjects will receive one IV infusion of docetaxel, using the MTD identified in Cohort 1, followed by one IV infusion of placebo. An additional placebo infusion (without docetaxel) will be given on approximately Day 8 of Cycle 1 only.

Crossover from Arm A to Arm B and vice versa will not be allowed.

Phase 2b Randomized Phase will enroll approximately 160 subjects.

Phase 1, Phase 2, and Phase 2b Assessments

Clinical response assessments will be performed every 9 weeks  $\pm$  1 week (i.e., every third cycle beginning at the Screening visit) until disease progression or lack of tolerability. Response assessments will be reported by the investigator and reviewed by the Medical Monitor.

Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. Docetaxel treatment beyond 12 cycles of therapy may be considered at the discretion of the treating investigator and Medical Monitor, and after a careful assessment and discussion of risk versus benefit with the subject. Study activities are summarized in [Table 1](#).

**Number of Subjects Planned:**

Approximately 300 subjects will be enrolled in the study (approximately 20 in Phase 1b, 40 in Phase 2 [20 subjects per cohort], and 240 in Phase 2b [up to 80 subjects in Monotherapy Expansion, and 160 subjects in Randomized Phase].

**Diagnosis and Criteria for Inclusion and Exclusion:**

Disease Specific Inclusion Criteria:

1. Stage IV, locally advanced or metastatic (T4b, any N; or any T, N2-3) urothelial bladder cancer or transitional cell carcinoma (TCC) arising in another location of the urinary tract, including urethra, ureter, and renal pelvis
2. Histological or cytological diagnosis of UCC. Mixed histologies are permitted as long as TCC is the major component (i.e., > 50% of the pathologic specimen). Pure or predominant squamous cell carcinomas or adenocarcinomas are not permitted
3. Relapsed after or are refractory to at least one prior line of chemotherapy which have not included a taxane (with the exception of Cohort 3 of Phase 2 and Phase 2b Monotherapy Expansion which will allow the enrollment of subjects with prior treatment with a taxane)
4. Subjects must have received at least one prior chemotherapeutic regimen (at least one cycle each) for advanced or metastatic/recurrent disease, of which at least one regimen included a platinum agent. If a platinum agent is contraindicated for a subject (e.g., due to pre-existing renal impairment such as creatinine clearance < 60 mL/min, myelosuppression, hearing impairment, or history of allergic reaction to platinum-

containing compounds), the prior regimen(s) need not have included a platinum agent. Reason for platinum contraindication will be collected in the eCRFs

5. Prior neoadjuvant or adjuvant chemotherapy (without a taxane, except Cohort 3 of Phase 2 and Monotherapy Expansion of Phase 2b which will allow the enrollment of subjects with prior treatment with a taxane) is permitted and will not be counted as first-line chemotherapy, as long as the subject has not progressed within 12 months of the last dose. However, if the patient progressed within 12 months of the last dose of prior neoadjuvant or adjuvant chemotherapy, then this regimen of neoadjuvant or adjuvant chemotherapy will be counted as first-line chemotherapy
6. Measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1; see [Appendix 3](#)). If possible, sites of measurable disease should not be within a previously irradiated site. However, if all sites of measurable disease have been irradiated, at least one site must have demonstrated growth after irradiation
7. Subjects must be anticipated to have a PFS of at least 4 weeks from the time of randomization (i.e., tumor progression per RECIST v1.1 is not anticipated within the first 4 weeks after randomization)

Phase 2 and Phase 2b Specific Inclusion Criteria:

1. Tumor shown to have at least one of the following FGFR3 mutations: R248C, S249C, G370/2C, S371/3C, Y373/5C, G380/82R, F384/6L, K650/2X (X=E,T or M) or FGFR3-TACC3 fusion, as shown by tests performed by a CAP or CLIA certified laboratory (or equivalent outside of the US) such as Foundation Medicine, Ashion Analytics, or Paradigm Diagnostics on samples that were obtained at or after the time when the subject was found to have muscle invasive disease or high grade papillary non-muscle invasive disease. In the absence of pre-existing genetic test results, subjects can submit archival tissue (obtained at or after the time subject was found to have muscle invasive disease) for genetic testing. When such archival tissue is not immediately available, a blood sample may be submitted for initial determination of FGFR3 mutation and/or fusion status. In all cases, subsequent to subject enrollment, previous test results that were not provided by Foundation Medicine will be verified using archival tissue (if not available for Randomized Phase, a core biopsy may be obtained). Blood samples will be obtained on Cycle 1 Day 1 to verify results observed in archival tissues or core biopsies.
2. Relapsed after or are refractory to an immune checkpoint inhibitor (such as atezolizumab, pembrolizumab, nivolumab, avelumab, or durvalumab). This inclusion criterion does not apply if the checkpoint inhibitor is contraindicated. Reason for checkpoint inhibitor contraindication will be collected in the eCRFs. If a checkpoint inhibitor is not an approved or available therapy for UCC, then this inclusion criterion does not apply.

General Inclusion Criteria:

1. Signed informed consent form, including:
  - a. Consent to provide tumor tissue and blood samples for genetic testing

- b. Consent to provide metastatic tumor tissue during the study, if available, or at autopsy for testing of FGFR3 status, as well as other potential biomarkers
  - c. Consent to provide survival information after completion of study drug dosing
- 2. For Cohort 1, archival tumor samples must be available for retrospective sequencing of cancer-related genes, including FGFR3, by NGS. For Cohorts 2 and 3 of Phase 2 and all subjects in Monotherapy Expansion and (Randomized Phase, subjects must be confirmed to have a FGFR3 genomic alteration at the time of documentation of advanced disease. Available tissue that was obtained at or after the time the subject was found to have muscle invasive disease and is of suitable quality and quantity (as outlined in the Sponsor's Laboratory Instructions) should be used to assess the FGFR3 status by genetic testing. A blood sample to assess the FGFR3 status of circulating tumor DNA by genetic sequencing must also be provided. (described in Section 6.2.2). In case no archival tissue sample is available or tissue testing was not informative, a blood sample to assess the FGFR3 status by circulating tumor DNA (ctDNA) can be submitted and if positive will be considered adequate for inclusion. For subjects participating in Phase 2b Monotherapy Expansion Phase and Phase 2b Randomized Phase, if suitable archival tissue is unavailable and ctDNA is not informative, then a core biopsy of tumor tissue (metastatic or primary from any anatomical location except the bone, lung or brain) can be obtained to determine FGFR3 status.
- 3. Age  $\geq 18$  years ( $\geq 20$  years in Taiwan)
- 4. Life expectancy  $\geq 12$  weeks
- 5. Presence of less than 3 of the following 3 poor prognostic factors:
  - a. Eastern Cooperative Oncology Group (ECOG) performance status (PS)  $\geq 1$ ,
  - b. hemoglobin  $< 10$  g/dL, and
  - c. presence of liver metastasis

(Note: presence of all 3 poor prognostic factors correlates with rapid progression and a median survival of 1.7 months ([Bellmunt 2010](#); see also Figure 1)
- 6. ECOG PS of 0 or 1 (see [Appendix 1](#))
- 7. Adequate hematologic and end organ function defined by the following laboratory results obtained within two weeks prior to the first dose of study treatment:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelet count  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9.0$  g/dL without transfusion
  - d. Albumin  $\geq 2.5$  g/dL
  - e. Total bilirubin  $\leq$  upper limit of normal (ULN) (without exception, as stated in the docetaxel package insert)
  - f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)  $\leq 2.5 \times \text{ULN}$ , with the following exceptions:

<ul style="list-style-type: none"><li>– Subjects with documented bone metastases: <math>ALP \leq 5 \times ULN</math></li><li>– Note: Subjects with AST and/or ALT <math>&gt; 1.5 \times ULN</math> concomitant with alkaline phosphatase <math>&gt; 2.5 \times ULN</math> will not be allowed to enroll, regardless of presence of liver or bone metastases, as stated in the docetaxel package insert</li></ul> <p>g. Creatinine clearance <math>\geq 30</math> mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:</p> $\frac{(140 - age) \times (weight\ in\ kg) \times (0.85\ if\ female)}{72 \times (serum\ creatinine\ in\ mg/dL)}$ <p>h. Prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT) must be <math>\leq 1.5 \times ULN</math></p> <p>8. Willingness to avoid pregnancy or fathering children based on the criteria below:</p> <ul style="list-style-type: none"><li>a. Women of non-childbearing potential (i.e., surgically sterile with a hysterectomy and/or bilateral oophorectomy OR chemically sterile OR <math>\geq 12</math> months of amenorrhea in the absence of chemotherapy, anti-estrogens, or ovarian suppression). Women of non-childbearing potential need not undergo pregnancy testing</li><li>b. Women of childbearing potential who have a negative urine or serum pregnancy test at Screening and before the first dose of study drug on Cycle 1, Day 1, and who agree to take appropriate precautions to avoid pregnancy (with approximately 99% certainty) from Screening through 90 days after the last dose of study drug. Permitted methods of contraception that are approximately 99% effective in preventing pregnancy are described in <a href="#">Appendix 6</a>, should be communicated to the subject, and the subject's understanding confirmed</li><li>c. Men who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from Screening through 90 days after the last dose of study drug. Permitted methods of contraception that are approximately 99% effective in preventing pregnancy are described in <a href="#">Appendix 6</a>, should be communicated to the subject, and the subject's understanding confirmed</li></ul> <p>9. Negative urine or serum pregnancy test within 3 days prior to randomization in women of childbearing potential</p> <p>10. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule (such conditions should be discussed with the subject before study entry)</p>	
<p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"><li>1. Prior use of any other investigational drug (i.e., monoclonal antibody or experimental therapy) within 2 weeks before Cycle 1, Day 1</li><li>2. Palliative radiotherapy within 2 weeks prior to Cycle 1, Day 1</li></ul>	



3. Prior anti-cancer therapy (e.g. biologic or other targeted therapy, chemotherapy or hormonal therapy) within 2 weeks prior to Cycle 1, Day 1
  - a. A washout of less than 14 days may be allowed after discussion with the Medical Monitor, provided that the subject has recovered from any clinically relevant toxicity (Exception: participants with neuropathy of Grade 1 will be allowed study entry)
  - b. Clinical AEs, except for alopecia, from any previous treatments must have resolved to  $\leq$  Grade 1
  - c. Laboratory AEs from any previous treatments must have resolved to  $\leq$  Grade 1 or to within 10% of baseline prior to Cycle 1, Day 1
4. Prior treatment with an inhibitor that is targeted primarily to FGFRs
5. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
6. Inability to be pre-medicated with a corticosteroid when treated with docetaxel
7. Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association (NYHA) Class III or IV cardiac disease (see [Appendix 2](#)), myocardial infarction or stroke within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
8. History of major bleeding (requiring a blood transfusion  $\geq$  2 units) not related to a tumor within the past 12 months
9. History of clinically significant coagulation or platelet disorder in the past 12 months
10. Currently receiving anticoagulation treatment
11. Incomplete healing from wounds from prior surgery; wound is larger than 2 cm in length 28 days prior to randomization
12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at screening. Any major episode of infection requiring treatment with IV antibiotics or hospitalization must be resolved (including the completion of the course of antibiotics) prior to Cycle 1, Day 1
13. History of other malignancy which could affect compliance with the protocol or interpretation of results
14. Subjects with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed
15. Subjects with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for  $\geq$  2 years prior to Cycle 1, Day 1
16. Subjects with localized prostate cancer that has been treated with curative intent will be allowed

17. Presence of positive test results for Hepatitis B (Hepatitis B surface antigen [HBsAg] and/or total Hepatitis B core antibody [anti-HB-c]) or Hepatitis C (Hepatitis C virus [HCV] antibody serology testing)  
Subjects positive for anti HB-c are eligible only if polymerase chain reaction (PCR) is negative for Hepatitis B viral (HBV) deoxyribonucleic acid (DNA)
18. Known history of human immunodeficiency virus (HIV) seropositive status
19. Primary central nervous system (CNS) malignancy, or CNS metastases
20. Pregnancy (positive pregnancy test), lactation or breastfeeding
21. Inability to comply with study and follow up procedures
22. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications

### **Experimental Arm, Dose, and Mode of Administration:**

Vofatamab will be provided as a sterile lyophilized powder in 20-mL single-use vials. Vofatamab will be reconstituted with sterile water for injection, and the drug product will be delivered at a final concentration of at least 3 mg/mL. Phase 2b sterile liquid formulation of vofatamab in 20-mL single use vials is currently in development with planned concentration of approximately 50 mg/mL. Details will follow in the Investigational Medicinal Product Dossier (IMPD) and pharmacy manual at time of introduction of this new formulation.

#### Phase 1b

- Cohort 1: Subjects will receive one IV infusion of docetaxel, 75 mg/m<sup>2</sup>, over approximately 60 minutes; followed by one IV infusion of vofatamab, 25 mg/kg, on Day 1 of each 21-day cycle. The vofatamab infusion should begin approximately 30 minutes after completion of the docetaxel infusion, and should be administered over 90 (± 15) minutes to well-hydrated subjects. An IV loading dose of vofatamab, 25 mg/kg, (without docetaxel) will be given on approximately Day 8 of Cycle 1 only. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post infusion.

#### Phase 2

- Cohort 2: Subjects will receive one IV infusion of docetaxel, 75 mg/m<sup>2</sup>, over approximately 60 minutes; followed by one IV infusion of vofatamab, 25 mg/kg, on Day 1 of each 21-day cycle. The vofatamab infusion should begin approximately 30 minutes after completion of the docetaxel infusion, and should be administered over 90 (± 15) minutes to well-hydrated subjects. An IV loading dose of vofatamab, 25 mg/kg, (without docetaxel) will be given on approximately Day 8 of Cycle 1 only. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post infusion.
- Cohort 3: Subjects will receive one IV infusion of vofatamab, 25 mg/kg, on Day 1 of each 21-day cycle. The vofatamab infusion should be administered over 90 (± 15) minutes to well-hydrated subjects. An IV loading dose of vofatamab, 25 mg/kg, will be given on approximately Day 8 of Cycle 1 only. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post infusion.

#### Phase 2b

- Monotherapy Expansion: Subjects will receive one IV infusion of vofatamab, 25 mg/kg, on Day 1 of each 21-day cycle. The vofatamab infusion should be administered over 90 (± 15) minutes to well-hydrated subjects. An IV loading dose of vofatamab, 25 mg/kg, will be given on approximately Day 8 of Cycle 1 only. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be

administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion.

- **Phase 2b Randomized Phase:** Subjects in Arm A will receive one IV infusion of docetaxel, over approximately 60 minutes, followed by one IV infusion of vofatamab, using the MTD identified in Cohort 1 of the Phase 1b, on Day 1 of each 21-day cycle. The vofatamab infusion should begin approximately 30 minutes after completion of the docetaxel infusion; and the initial dose of vofatamab will be administered over 90 ( $\pm$  15) minutes to well-hydrated subjects. An additional IV loading dose of vofatamab, using the dose identified in Cohort 1 of the Phase 1b (without docetaxel) will be given on approximately Day 8 of Cycle 1 only. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion.

**Control Arm, Dose, and Mode of Administration:**

Placebo will be provided as a sterile liquid formulation in 20-mL single-use vials in identical format to vofatamab.

Subjects in Arm B of Randomized Phase of Phase 2b will receive one IV infusion of docetaxel at a dose based on the MTD identified in Cohort 1 of Phase 1b over approximately 60 minutes, followed by one IV infusion of placebo on Day 1 of each 21-day cycle. The placebo infusion should begin approximately 30 minutes after completion of the docetaxel infusion, and the initial infusion of placebo will be administered over 90 ( $\pm$  15) minutes to well-hydrated subjects. If prior infusions have been well-tolerated, subsequent infusions of placebo may be administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion.

An additional IV infusion of placebo (without docetaxel) will be given on approximately Day 8 of Cycle 1 only.

**Premedication:**

Premedication with a corticosteroid will be administered according to the site's institutional standard. An acceptable regimen may consist of dexamethasone 8 mg orally, twice-a-day, for 3 days, beginning one day prior to docetaxel infusion. Other premedications, such as anti-emetics or antihistamines, may be prescribed, as needed, based on the investigator's assessment.

**Statistical Methods:**

Phase 1b and Phase 2:

Descriptive statistics will be utilized to present the MTD, safety, and efficacy results for the Phase 1b and Phase 2 by cohort. The remaining subsections will focus on Phase 2b Monotherapy Expansion and Randomized Phases.

Phase 2b Monotherapy Expansion Phase:

The primary efficacy outcome measure will be PFS, defined as the time from randomization to first occurrence of disease progression (per RECIST v1.1) or death, whichever occurs first. If a subject does not experience progressive disease (PD) or death, PFS will be censored at the day of the last adequate tumor assessment. PFS will be reported by the Investigator at each site and confirmed by the Medical Monitor.

The analysis of the primary efficacy endpoint of PFS will be based on subjects who received at least one dose of vofatamab. The Kaplan-Meier (KM) curves will be presented for Monotherapy Expansion with calculation of median time (months) and its 95% confidence limits.

The analysis method for PFS will be utilized for overall survival (OS), the key secondary endpoint. One sample log-rank test for the median OS in the vofatamab versus historical median OS of 7 months will be performed.

In addition, best overall response will be summarized. The number and percentage of subjects who had confirmed complete response (CR) or partial response (PR) as assessed by the investigator using RECIST 1.1 criteria will be provided for subjects who received at least one dose of vofatamab.

Safety data including ATAs, AEs, changes in key laboratory test results, ECGs, and changes in vital signs will be summarized for subjects who received at least one dose of vofatamab.

At participating sites, an intensive PK Sub-study for up to 10 subjects in who provided separate informed consent ([Appendix 8](#)) will be performed. Plasma concentrations of vofatamab over time will be summarized using descriptive statistics. PK parameters (e.g.,  $C_{max}$ , AUC,  $t_{1/2}$ ) may be listed and summarized using descriptive statistics.

Phase 2b Randomized Phase:

*Primary Efficacy Endpoint Analysis:*

The primary efficacy outcome measure will be PFS, defined as the time from randomization to first occurrence of disease progression (per RECIST v1.1) or death, whichever occurs first. If a subject does not experience progressive disease (PD) or death, PFS will be censored at the day of the last adequate tumor assessment. PFS will be reported by the Investigator at each site and reviewed by the Medical Monitor.

The analysis of the primary efficacy endpoint of PFS will be based on the intent-to-treat (ITT) population. The Kaplan-Meier (KM) curves will be presented for each treatment arm with calculation of median time (months) and its 95% confidence limits.

The hypothesis test of the primary efficacy endpoint will be performed using an overall two-sided significance level of 0.025. The stratified log-rank test with a covariate to control for the stratification factor of visceral metastasis (present versus absent) will be performed on the ITT population to test the superiority of Arm A over Arm B.

A sensitivity analysis will also be performed on the Efficacy Evaluable (EE) analysis set (if applicable).

*Secondary Efficacy Endpoint Analyses:*

To maintain an upper boundary on the overall experiment-wise type I error rate, hypothesis testing of the secondary efficacy endpoints on the ITT population will follow a closed testing procedure. Inferential comparisons between treatment groups for one or more of the following efficacy endpoints, listed in rank order of importance, will be made provided the null hypothesis associated with the final analysis of PFS is rejected at the statistical significance level of two-sided 0.025.

Rank order of efficacy endpoints for analyses:

1. PFS (Primary Endpoint)
2. OS (Key Secondary Endpoint)
3. ORR

Inferential testing of the secondary efficacy endpoints will proceed in a sequential step-down manner, provided the null hypothesis associated with the previously tested endpoint is rejected at the pre-defined statistical significance level. Otherwise, no further inferential testing will be conducted.

If formal inferential statistical testing is stopped due to the closed testing procedure, inferential statistics may be employed for the remaining secondary efficacy endpoints.

Definitions of Secondary Endpoints:

- ORR is defined as the percentage of subjects who have baseline measurable disease and who achieve a best response of either complete response (CR) or partial response (PR) as assessed by the investigator using RECIST 1.1 criteria. Subjects who do not achieve a CR or PR will be counted as a non-responder.
- OS defined as the time from randomization to death from any cause. For subjects who are alive at the time of analysis data cutoff, OS time will be censored at the last date the subject was known to be alive. Survival time for subjects with no post-baseline survival information will be censored on the date of randomization.
- Median time to response (TTR) defined as the time to the first occurrence of a documented response.
- Duration of objective response, defined as the first occurrence of a documented, objective response until the time of relapse or death from any cause. This will be calculated only for subjects who had a confirmed overall response of CR or PR. In the absence of confirmation of death or progressive disease, duration of response will be censored at the last adequate disease assessment date.
- DCR defined as the percentage of subjects who achieve either CR or PR or stable disease (SD), as assessed by the investigator per RECIST v1.1.
- DCR (90), defined as the absence of disease progression and death 90 days from the time of randomization as assessed by the investigator using RECIST v1.1.

- DCR (150), defined as the absence of disease progression and death 150 days from the time of randomization as assessed by the investigator using RECIST v1.1.
- QOL, as assessed by EORTC QLQ-C30 (in Phase 2b: Cohorts 4 and 5 [Monotherapy Expansion and Randomized Phase, respectively]) will be scored per standard methodology developed for the survey. Results will be compared between treatment groups; changes from baseline will also be calculated. Ad hoc analyses of individual questions relevant to side effects from each treatment may also be performed.

The time-to-event (OS, TTR, DOR) variables will be summarized by the method described for PFS except that DOR will be based on responders.

For categorical response variables (i.e., ORR, DCR), the frequency count, percentage, and 95% confidence intervals will be summarized for subjects randomized to the two treatments. The response rates will be compared between the randomized groups via the stratified Cochran-Mantel-Haenszel test based on the ITT population.

#### Exploratory Endpoints

The association between FGFR3 mutations or fusions and other biomarkers and efficacy and AE outcomes will be explored.

Plasma concentrations of vofatamab over time will be summarized using descriptive statistics. PK parameters (e.g., C<sub>max</sub>, AUC, t<sub>1/2</sub>) may be listed and summarized using descriptive statistics.

#### *Safety Endpoint Analysis:*

Safety will be assessed through summaries of AEs, changes in key laboratory test results, ECGs, and changes in vital signs. The number and percentage of subjects with confirmed positive ATA will be summarized descriptively by scheduled time point. All subjects who receive any amount of vofatamab or docetaxel will be included in the safety analysis.

The safety data will be presented by treatment study arm in individual subject listings and summary tables.

#### *Interim Analyses:*

No formal interim analysis is planned for Phase 2b Monotherapy Expansion and Randomized Phases.

#### *Safety Review:*

Safety analyses will be performed by a vofatamab Safety Oversight Committee (SOC) for phase 1b, phase 2 and Monotherapy Expansion of phase 2b and by study-specific Data Monitoring Committee (DMC) for Randomized Phase of Phase 2b based on guidelines outlined in the SOC and DMC Charters. The safety review will include AE as well as laboratory and ECG data. The safety assessments during Phase 1b, Phase 2 and Monotherapy Expansion of Phase 2b will be conducted in an open fashion. The safety assessments during the Randomized Phase will be conducted in a blinded fashion on treatment arm and aggregate data. Unblinding in the Randomized Phase will only occur if deemed necessary by the DMC and then only on an individual subject basis.

#### Sample Size Determination for All Phases

Phase 2 has two cohorts of 20 subjects each (Cohorts 2 and 3). At the end of Cohort 3 of Phase 2 (N = 20), there is approximately 88% power to detect a difference between a median PFS of 5.5 months in vofatamab monotherapy arm versus 2.5 months from historical data using one sample log-rank test at one-sided alpha level of 0.025 (Finkelstein, 2003; Woolson, 1981; Lachin, 1986).

The planned sample size for Phase 2b Monotherapy Expansion (up to 80 subjects) is mainly based on the safety requirement, with the power to detect a difference between a median OS of 12.0 months in vofatamab monotherapy arm versus 7.0 months from historical data being approximately 97% using a one sample log-rank test at one-sided alpha level of 0.025.

The primary efficacy endpoint of the Phase 2b Randomized Phase is designed to compare PFS in subjects with UCC who are treated with vofatamab plus docetaxel versus placebo plus docetaxel. The planned sample size of approximately 160 subjects (107 treated with vofatamab plus docetaxel and 53 treated with placebo plus docetaxel) will provide 99% power to detect a difference between a median PFS of 5.5 months in vofatamab plus docetaxel arm versus 2.5 months in the placebo plus docetaxel arm (hazard ratio = 0.46) at alpha = 0.025 (one-sided). This also assumes a 24-month accrual period, 12-month follow-up, 10% of dropout rate within 2 years, and an exponential distribution of PFS event times. In addition, this sample size has approximately 97% power to detect a difference between a median OS of 15 months in vofatamab plus docetaxel arm versus 7.0 months in the placebo plus docetaxel arm (hazard ratio = 0.47).



**Table 1 Schedule of Assessments**

	Screening	Phases 1b, 2, and 2b				End of Treatment/ ET Visit <sup>a,c</sup>	
		Cycle 1 (Weeks 1 - 3) <sup>a,b</sup>			Cycles 2+ (until progression) <sup>a,b</sup>		
	Days -28 to -1	Day 1	Day 8	Day 15	Day 1 (= Day 21 of Previous Cycle)		
Written informed consent <sup>d</sup>	X						
Confirm availability and request archival tumor tissue <sup>e</sup>	X						
FGFR3 central testing <sup>e</sup>	X						
Review inclusion/exclusion criteria <sup>f</sup>	X						
Medical history and demographics	X						
Complete physical examination <sup>g</sup>	X						
Targeted physical examination <sup>g</sup>		X			X	X	
Height (screening only) and weight	X	X	X		X	X	
Vital signs <sup>h</sup>	X	X	X		X	X	
ECOG performance status	X	X			X	X	
Adverse events <sup>i,j</sup>		X	X <sup>i</sup>		X	X <sup>j</sup>	
Concomitant medications	X	X	X		X	X	
Tumor assessment <sup>k,l</sup>	X <sup>k</sup>				X <sup>l</sup>	X <sup>l</sup>	
Hematology <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X <sup>m</sup>	X	
Serum chemistry <sup>n</sup>	X	X			X	X	
Electrocardiogram <sup>o</sup>	X	X			X <sup>o</sup>	X	
Coagulation (aPTT, PT/INR, fibrinogen) <sup>p</sup>	X	X	X		X	X	
Urine or Serum pregnancy test <sup>q</sup>	X	X			X	X	
HBV and HCV screening <sup>r</sup>	X						
Urinalysis <sup>s</sup>	X	X			X		

	Screening	Phases 1b, 2, and 2b				End of Treatment/ ET Visit <sup>a,c</sup>	
		Cycle 1 (Weeks 1 - 3) <sup>a,b</sup>		Cycles 2+ (until progression) <sup>a,b</sup>			
	Days -28 to -1	Day 1	Day 8	Day 15	Day 1 (= Day 21 of Previous Cycle)		
Urine and blood biomarker sampling <sup>t</sup>		X			X	X	
PK <sup>u</sup>		X	X		X	X	
ATA <sup>v</sup>		X			X	X	
PK Sub-Study <sup>w</sup>		X	X	X	X	X	
PROMIS GPH Short Survey <sup>x</sup>	X				X	X	
EORTC QLQ-C30 <sup>y</sup>	X				X	X	
Survival (via visits or telephone contact)		X	X		X	X	X <sup>z</sup>
Study drug infusion		X <sup>aa</sup>	X <sup>aa</sup>		X <sup>aa</sup>		

aPTT = activated partial thromboplastin time; ATA = anti-vofatamab antibodies; ECOG = Eastern Cooperative Oncology Group; ET = early termination; GPH = Global Physical Health; HBV = hepatitis B virus; HCV = hepatitis C virus; IHC = immunohistochemistry; INR = international normalized ratio; NGS = Next Generation Sequencing; PK = pharmacokinetics; PT = prothrombin time.

- <sup>a</sup> Study visits may occur  $\pm$  3 days from the date scheduled if required for logistical/scheduling reasons.
- <sup>b</sup> Local laboratory assessments (i.e., hematology, coagulation, serum chemistry, viral serology, urine or serum pregnancy testing, and urinalysis) may be performed within 72 hours preceding study drug administration unless otherwise specified.
- <sup>c</sup> Perform within 30 days after the last infusion of study drug.
- <sup>d</sup> Informed consent form(s) must be signed by the subject before any study-specific procedures are performed.
- <sup>e</sup> For Cohort 1, archival tumor samples must be available for retrospective sequencing of cancer-related genes, including FGFR3, by NGS. For Cohorts 2 and 3 of Phase 2 and all subjects in Monotherapy Expansion and Randomized Phase, subjects must be confirmed to have a FGFR3 genomic alteration at the time of documentation of advanced disease. Available tissue that was obtained at or after the time the subject was found to have muscle invasive disease and is of suitable quality and quantity (as outlined in the Sponsor's Laboratory Instructions) should be used to assess the FGFR3 status by genetic testing. A blood sample to assess the FGFR3 status of circulating tumor DNA by genetic sequencing must also be provided (described in [Section 6.2.2](#)). In case no archival tissue sample is available or tissue testing was not informative, a blood sample to assess the FGFR3 status by circulating tumor DNA (ctDNA) can be submitted and if

positive will be considered adequate for inclusion. For subjects participating in Phase 2b Monotherapy Expansion and Randomized Phase, if suitable archival tissue is unavailable and ctDNA is not informative, then a core biopsy of tumor tissue (metastatic or primary from any anatomical location except the bone, lung or brain) can be obtained to determine FGFR3 status.

- <sup>f</sup> The inclusion and exclusion criteria are the same for all subjects enrolled in the study, except Cohort 1 of the Phase 1b will enroll subjects with UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy while Cohorts 2 and 3 of Phase 2b and Phase 2b Monotherapy Expansion and Randomized Phase of Phase 2b will enroll subjects with UCC positive for FGFR3 mutation and/or fusion who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy.
- <sup>g</sup> Complete physical exam includes all systems described in the body of the protocol. The targeted physical exam should only include systems of most clinical relevance (i.e., cardiovascular, respiratory, and those associated with clinical signs/symptoms).
- <sup>h</sup> Blood pressure (supine or sitting), pulse rate, and temperature. On Cycle 1 Day 1 and Cycle 1 Day 8, vital signs for vofatamab should be assessed pre-infusion, every 15 ( $\pm$  5) minutes during the infusion, at the end of the infusion, and 30 ( $\pm$  10) minutes, 60 ( $\pm$  10) minutes, and 90 ( $\pm$  10) minutes post-infusion. On subsequent cycles, vital signs for vofatamab should be assessed pre-infusion and as clinically indicated and post-infusion. For infusions with docetaxel, vital signs should be assessed per institutional guidelines, or regional label. Vital signs also will be measured at the End of Treatment/ET visit.
- <sup>i</sup> Subjects will be monitored for any untoward effects during study drug infusion, for 90 minutes following completion of the infusion on Day 1 of Cycle 1, and for 30 minutes in the absence of infusion-related adverse events (AEs) at subsequent infusions. All AEs will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.
- <sup>j</sup> Follow-up for AEs will occur for 30 days after the subject's last dose of study drug or until initiation of another anti-tumor therapy, whichever occurs first.
- <sup>k</sup> All evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. A documented standard-of-care tumor assessment performed within 28 days prior to Cycle 1, Day 1 may be used for the screening assessment. For subjects with measurable disease, response will be reported by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v 1.1; see [Appendix 3](#)) and reviewed by the Medical Monitor. Screening assessments must include: (1) computerized tomography (CT) scans of the chest, abdomen, and pelvis and all known or suspected sites of disease, and (2) brain scan (CT or magnetic resonance imaging [MRI]). At the investigator's discretion, additional methods of assessment of measurable disease per RECIST v1.1 may be used in addition to those listed above. For subsequent tumor assessments, a CT scan of the chest, abdomen, and pelvis, and all known or suspected sites of disease must be obtained each time. The same imaging methods used at screening must be used throughout the study for each subject.
- <sup>l</sup> Perform tumor assessments every 9 weeks  $\pm$  1 week and prior to start of next infusion (i.e., every third cycle beginning at the Screening visit) until disease progression or lack of tolerability. Additional tumor assessments may be conducted as clinically indicated during the study. Results must be reviewed prior to study drug infusion at next cycle and continuation in the study will be based on the tumor assessment results. A tumor assessment scan should be performed if the subject is discontinuing the study early. At the End of Treatment/ET visit, subjects will be asked to provide an optional metastatic tumor tissue sample (biopsy) at End of Treatment or at autopsy.

- <sup>m</sup> Includes complete blood count (hemoglobin, hematocrit, red blood cell [RBC] count, white blood cell [WBC] count), platelet count, and percent and absolute differential counts (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells). For the Phase 1b, Phase 2 and Phase 2b, CBC will be obtained on Day 1 of each cycle and on Day 8 (+/- 2 days) of Cycle 1. For the Phase 1b and Phase 2, CBC will also be obtained on Day 15 (+/- 2 days) of Cycle 1.
- <sup>n</sup> Includes sodium, potassium, chloride, bicarbonate, non-fasting glucose, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and uric acid.
- <sup>o</sup> Subjects should be resting in a supine or sitting position for  $\geq 10$  minutes prior to electrocardiogram (ECG) collection. One ECG reading should be obtained at each of the following time points: Screening; Cycle 5, Day 1 (prior to infusion with study drug); and at the End of Treatment visit. ECGs (at least 3 readings) should be obtained at the following time points: Cycle 1, Day 1 (prior to infusion with study drug; 30 ( $\pm 15$ ) minutes and 2-hours ( $\pm 15$  minutes) post infusion with study drug) and Cycle 2, Day 1 (prior to infusion with study drug).
- <sup>p</sup> Coagulation assessments (activated partial thromboplastin time [aPTT], prothrombin time [PT]/international normalization ratio [INR], and fibrinogen).
- <sup>q</sup> For women of childbearing potential, a urine or serum pregnancy test must be performed at Screening, prior to administration of study drug on Day 1 of each cycle, and at the End of Treatment/ET visit.
- <sup>r</sup> Hepatitis B surface antigen, Hepatitis B core antibody, and Hepatitis C antibody (HBcAb) serology required at Screening (also Hepatitis B viral deoxyribonucleic acid [DNA] by polymerase chain reaction [PCR] if the subject is HBcAb positive).
- <sup>s</sup> Urinalysis includes macroscopic analysis (specific gravity, pH, protein, glucose, ketones, blood, bilirubin, leukocyte esterase, urobilinogen, and nitrite) and microscopic urinalysis (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast).
- <sup>t</sup> Urine samples for assessment of biomarkers will be collected pre-dose on Cycle 1, Day 1. Samples will be collected within 60 minutes following study drug (vofatamab or placebo) infusion on Day 1 of Cycles 2 and 5. Blood for circulating tumor DNA (ctDNA) will be collected at the time of progression. Urine will also be collected for assessment of biomarkers at EOT.
- <sup>u</sup> Serum samples for assessment of vofatamab pharmacokinetics (PK) will be drawn within 30 ( $\pm 15$ ) minutes after completion of docetaxel infusion and before study drug (vofatamab or placebo) infusion and within 30 ( $\pm 15$ ) minutes after the end of study drug (vofatamab or placebo) infusion on Days 1 and 8 of Cycle 1, Day 1 of Cycles 2, 5, and 10 and once at the End of Treatment/Early Termination (ET) visit.
- <sup>v</sup> Serum samples for assessment of anti-vofatamab antibodies (ATAs) will be drawn prior to study drug (vofatamab or placebo) infusion on Day 1 of Cycles 1, 5 and at the End of Treatment/ET visit.
- <sup>w</sup> Pharmacokinetic Sub-study: up to 10 subjects at designated centers in Phase 2b Monotherapy Expansion who provide separate informed consent ([Appendix 8](#)) will participate in a PK Sub-study and will have intensive PK sample collection (samples obtained before and 30 minutes post-dosing) performed on Day 1 of Cycles 1, 2, 3, 5, 6, 10, and end of treatment following the initiation of vofatamab dosing. In addition, for Cycle 1, samples will be collected on Day 2 and 4, and on Day 8 before and 30 minutes post-dosing. In Cycle 5, samples will be collected on Day 2, Day 8, Day 15, and Day 21.

- <sup>x</sup> Administer the PROMIS GPH Short Survey during Phase 1b (cohort 1) and Phase 2 (cohort 2 and cohort 3) at the Screening visit, at the end of every third cycle (i.e., end of Cycles 3, 6, 9, and 12; or Week 9 and every 9 weeks thereafter for up to 36 weeks, before pre-medication and administration of the next dose) and at the End of Treatment/ET visit.
- <sup>y</sup> The EORTC QLQ-C30 instrument is administered during Cohorts 4 and 5 (Monotherapy Expansion and Randomized Phase, respectively) of Phase 2b at the Screening visit, at the end of every third cycle (i.e., end of Cycles 3, 6, 9, and 12; or Week 9 and every 9 weeks thereafter for up to 36 weeks, before pre-medication and administration of the next dose) and at the End of Treatment/ET visit.
- <sup>z</sup> All subjects will be followed for survival every 3 months via telephone until death or full withdrawal of consent. The End of Study survival assessment should be performed via telephone follow-up.
- <sup>aa</sup> Subjects in Cohorts 1 of Phase 1b and Cohort 2 of Phase 2 will receive one intravenous (IV) infusion of docetaxel followed by one IV infusion of vofatamab on Day 1 of each 21-day cycle. Subjects in Cohort 3 of Phase 2 and Phase 2b Monotherapy Expansion of Phase 2b of the study will receive an IV infusion of vofatamab on Day 1 of each 21-day cycle. Subjects in Randomized Phase of Phase 2b of the study will receive one IV infusion of docetaxel followed by one IV infusion of study drug (vofatamab or placebo), using the MTD identified in Cohort 1 of Phase 1b, on Day 1 of each 21-day cycle. Docetaxel will be administered over approximately 60-minutes. The initial infusion of study drug (vofatamab or placebo) should begin approximately 30 minutes after completion of the docetaxel infusion and should be administered over 90 ( $\pm$  15) minutes to well-hydrated subjects. If prior infusions have been well-tolerated, subsequent doses of study drug (vofatamab or placebo) may be administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion. An additional IV dose of study drug (vofatamab in Phase 1b, Phase 2, and Monotherapy Expansion of Phase 2b; vofatamab or placebo in Randomized Phase) will be given on approximately Day 8 of Cycle 1 only. Doses for Cycle 2 and beyond may be given  $\pm$  3 days from the date scheduled if required for logistical/scheduling reasons. Doses may also be delayed up to 21 days for recovery from reversible toxicity.

## GLOSSARY OF TERMS

Abbreviation/Acronym	Definition
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
anti-HB-c	Hepatitis B core antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-vofatamab antibodies
ATC	anatomical therapeutic chemical
AUC	area under the concentration curve
BUN	blood urea nitrogen
CBC	complete blood count
ctDNA	circulating tumor deoxyribonucleic acid
CHO	Chinese hamster ovary
CL	Clearance
CNS	central nervous system
CR	complete response
CRO	clinical research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of objective response
DVT	deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EE	efficacy evaluable
EORTC QLQ-C30	European Organization for Research and Treatment Quality of Life Questionnaire
ET	early termination
EU	European Union

<b>Abbreviation/Acronym</b>	<b>Definition</b>
FDA	Food and Drug Administration
FGFR3	fibroblast growth factor receptor 3
GCP	Good Clinical Practice
GPH	Global Physical Health
HBcAb	Hepatitis C antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	head, eye, ear, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IgG <sub>1</sub>	immunoglobulin G <sub>1</sub>
IHC	Immunohistochemistry
IRB/EC	Institutional Review Board/Ethics Committee
IRR	infusion-related reaction
ITT	intent-to-treat
IV	Intravenous
IVRS/IWRS	interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMP-1	matrix metalloproteinase-1
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetic
pro-MMP-10	pro-matrix metalloproteinase-10
PR	partial response

<b>Abbreviation/Acronym</b>	<b>Definition</b>
PS	performance status
PT/INR	prothrombin time/international normalized ratio
PTT	partial thromboplastin time
QOL	quality of life
QW	Weekly
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SDV	source data verification
SOC	Safety Oversight Committee
TCC	transitional cell carcinoma
TTR	time to response
UCB	urothelial cell carcinoma of the bladder
UCC	urothelial cell carcinoma
ULN	upper limit of normal
US	United States
vofatamab	formerly referred to as B-701 and MFGR1877S
WBC	white blood cell
WHO	World Health Organization
WT	wild-type



## 1 INTRODUCTION

### 1.1 Background on Urothelial Cell Carcinoma

Urothelial cell carcinoma (UCC; also known as transitional cell carcinoma [TCC]) occurs in the urinary system (i.e., kidneys, urinary bladder, and accessory organs) and is the most common type of bladder cancer, accounting for 90% of all bladder tumors (Eble 2004). It is the fifth most common cancer in the United States (US) (Costantini 2011) and fourth most common cancer in Europe (Jemal 2011); with an estimated 74,690 new cases and 15,580 deaths occurring in the US in 2014 (Cancer.org), and an estimated 136,000 new cases and 49,000 deaths occurring in Europe in 2009 (Bellmunt 2009).

Clinical and pathological studies have identified two variants of urothelial cell carcinoma of the bladder (UCB) which arise via distinct mechanisms, a low-grade papillary variant and an invasive tumor variant (Wu 2005, Vallot 2011). The low-grade papillary variant accounts for 80% of all UCBs and arises from urothelial hyperplasia. The five-year survival for this tumor type, when treated with surgery and intravesical immunotherapy, is greater than 90% (Cancer.org). The invasive tumor variant, which represents 20% of UCBs, has a poor prognosis, despite surgery and systemic therapy, with 50% of patients dying from metastasis within two years of diagnosis (Cancer.org). Furthermore, the five-year survival for metastatic bladder cancer is only 6%, and the median survival ranges from 8 to 15 months (Cancer.org). Therefore, while superficial tumors can be treated effectively with transurethral resection and intravesical therapy, there is a significant rate of recurrence and overall poor prognosis for patients with muscle invasive disease (Grossman 2003).

#### 1.1.1 *FGFR3 in Bladder Cancer*

The fibroblast growth factor receptor 3 (FGFR3) belongs to a family of structurally related tyrosine kinase receptors encoded by four different genes (FGFR1-4). These receptors regulate various biological processes, including proliferation, differentiation, migration and apoptosis.

Recent studies have shown that UCC tumors often have genetic alterations in FGFR3 (Cancer Genome Atlas Research Network 2013, Tomlinson 2007a, Gust 2013). Inappropriate FGFR3 signaling is implicated in the pathogenesis of the majority of muscle invasive UCC tumors with a notable percentage (16%–20%) caused by activating FGFR3 mutations or gene fusions, and a significant percentage (~50%) overexpressing the receptor (Gomez-Roman 2005, Tomlinson 2007a, Gust 2013). Preclinical data from several lines of investigation, including short hairpin ribonucleic acid knockdown (Tomlinson 2007b, Qing 2009), antibody targeting (Martinez-Torrecedrada 2005, Qing 2009), and small molecule inhibition (Lamont 2011) of FGFR3 in bladder cancer cell lines, also demonstrate that FGFR3 is essential for UCC cell growth in vitro and in vivo.

Mutations in two mutually exclusive isoforms of FGFR3, FGFR3-IIb the main form expressed in epithelial cells and FGFR3-IIc the main form expressed in chondrocytes (Murgue 1994, Delezoide 1998), have been identified in hematological cancers, multiple myeloma, and carcinomas of the bladder and cervix (Chesi 1997, Cappellen 1999, Richelda 1997). The

transforming properties of mutated FGFR3-IIIc, the main FGFR3 isoform expressed in multiple myeloma, are well documented (Chesi 2001, Ronchetti 2001). Additional studies have also demonstrated the oncogenic role of FGFR3-IIIb-S249C, the most common mutated form of FGFR3 in UCC (Bourdin 1999). In preclinical studies, the introduction of FGFR3-IIIb-S249C induced transforming properties characteristic of oncogenes, including anchorage-independent growth and tumor formation (Bernard-Pierrot 2005). Treatment with an FGFR kinase inhibitor, FGFR3 depletion, and siRNA in both the transformed FGFR3-S249c cells and a UCC cell line expressing a mutated form of FGFR3-IIIb, reversed the oncogenic properties of both cell lines; demonstrating that mutations in FGFR3-IIIb result in the oncogenic transformation of cells and are essential for UCC progression (Bernard-Pierrot 2005). More recently, two fusion forms of FGFR3, FGFR3- transforming acidic coiled-coil containing protein 3 (TACC3) and FGFR3-BAIAPL2, have been identified in bladder cancer and shown to have transformative properties (Williams 2013).

These data demonstrate the potential of FGFR3 as an important therapeutic target in the treatment of UCC of the bladder.

## **1.2 Background on Vofatamab**

Vofatamab is a phage-derived, affinity-matured, human monoclonal antibody specific for FGFR3. It is based on a human immunoglobulin G1 (IgG<sub>1</sub>) framework containing heavy chain V<sub>H</sub>III and light chain V<sub>k</sub>I subgroup sequences. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and two light chains (214 amino acid residues each) with inter- and intra-chain disulfide bonds that are typical of IgG<sub>1</sub> antibodies. The CH2 domain of each heavy chain also has a single conserved glycosylation site at Asn<sup>307</sup>. The N-linked oligosaccharides of vofatamab are typical of those observed on other CHO-derived monoclonal antibodies.

Vofatamab can be used to target FGFR3-positive tumors via three possible modes of action: (1) the blocking of ligand binding, receptor dimerization and activation, and downstream receptor signaling, (2) eliciting effector function such as antibody-dependent cell-mediated cytotoxicity (ADCC), and/or (3) antagonizing ligand-independent activating mutations (Qing 2009).

### **1.2.1 Nonclinical Data with Vofatamab**

In in vivo studies, vofatamab demonstrated binding to FGFR3 from multiple species, including mouse, rat, cynomolgus monkey, and human. Vofatamab also inhibited ligand binding to FGFR3, prevented receptor-receptor association, blocked receptor dimerization, and blocked downstream signaling from both wild-type (WT) and common mutant variants of FGFR3, as well as FGFR3-TACC3 fusions linked with bladder cancer. Vofatamab suppressed FGFR3-mediated cell proliferation and exerted strong anti-tumor activity in mouse xenograft models of both bladder carcinoma and t(4;14)-positive multiple myeloma. Anti-tumor activity was due to direct inhibition of FGFR3 signaling and/or engagement of ADCC.

Vofatamab was well-tolerated and resulted in no severe toxicities when administered intravenously weekly for 8 weeks (total of nine doses) in either rats or cynomolgus monkeys at doses up to the maximum feasible dose of 50 mg/kg. Vofatamab-related effects in the repeat-dose toxicity study in rats were limited to microscopic findings of minimal to slight focal tubular hypospermatogenesis/atrophy in male rats at the recovery necropsy. These observations were limited in distribution and severity, and therefore considered unlikely to result in a detectable impact on fertility. Vofatamab-related effects that were observed in cynomolgus monkeys included increased spleen weight and minimal/moderate splenic lymphoid hyperplasia at terminal necropsy. These effects were reversible and not considered adverse.

Pharmacokinetic (PK) studies of vofatamab in mice, Sprague-Dawley rats, and cynomolgus monkeys demonstrated both non-linear and linear PK characteristics, suggesting that the total clearance (CL) of vofatamab consists of contributions of a specific (target-mediated) CL component and a non-specific CL component, with the specific CL component having a greater contribution at lower doses. In repeat-dose toxicology studies in rats and cynomolgus monkeys, drug exposure increased proportionally with weekly (qw) intravenous (IV) doses of 5, 15, and 50 mg/kg, suggesting limited contribution of saturable target-mediated CL to the overall CL at these dose levels. Overall, the PK assessment indicates that vofatamab behaves like a typical IgG1, with some contribution of target-mediated clearance indicated by higher total CL estimates at the lower doses.

Additional nonclinical study information is provided in the Investigator's Brochure.

### **1.2.2            *Clinical Data with Vofatamab***

As of April 2013, two Phase 1 clinical studies of vofatamab have been completed, Study MFG4991g and Study MFG4809g. As of April 2018, an interim analysis of Cohort 1 in the Phase 1b of current study has been completed and is provided in [Section 1.2.2.3](#). Summaries of the respective studies are provided below and additional study information is provided in the Investigator's Brochure.

#### **1.2.2.1            Study MFG4991g (Phase 1 study in Patients with Advanced Solid Tumors)**

Study MFG4991g was an open-label, multicenter, Phase 1 study in 26 subjects with advanced solid tumors, of which 10 subjects had UCC. The safety and PK of escalating doses of vofatamab were evaluated following IV infusion of vofatamab to subjects once every 28 days (on Day 1 of each cycle), with an additional loading dose on Day 8 of Cycle 1 only. Doses of 2, 4, 8, 15, and 30 mg/kg of vofatamab were evaluated in 26 subjects. The study was terminated early by the Sponsor for reasons unrelated to efficacy or safety. All 26 subjects enrolled were in the dose-escalation stage, and the maximum tolerated dose was not reached. The maximum administered dose was 30 mg/kg on a 28-day schedule, and the median number of doses administered for all subjects was 3 (range 1-16).

Overall, vofatamab administered as an IV infusion at doses up to 30 mg/kg on a 28-day schedule was well-tolerated in subjects with advanced solid tumors. Two deaths due to disease progression were reported, and no deaths due to treatment-related AEs were reported. Only one

dose-limiting toxicity (DLT) was observed in the study; and was reported by one subject in the 30 mg/kg cohort (Grade 4 thrombocytopenia which occurred on Day 4 of treatment and was attributed by the investigator as possibly due to concomitant treatment with levofloxacin).

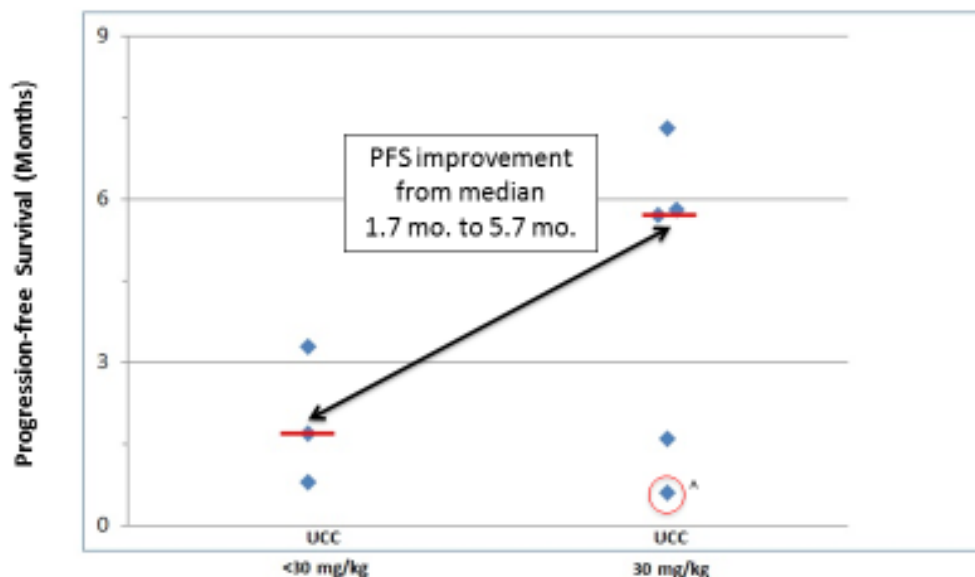
The adverse events (AEs) assessed as related to vofatamab and occurring in  $\geq 10\%$  of the subjects were fatigue (19.2%) and mucosal inflammation (11.5%). Furthermore, the majority of vofatamab-related AEs reported were Grade 1 or 2 in severity. Ten (38.5%) subjects experienced Grade  $\geq 3$  AEs, with 1 (3.8%) having Grade 4 thrombocytopenia and 1 (3.8%) having Grade 3 white blood cell (WBC) count decreased assessed as related to vofatamab. Eleven serious adverse events (SAEs) were reported in 8 (30.8%) subjects, with 1 (3.8%) subject experiencing one SAE assessed as related to vofatamab.

Serum exposure of vofatamab was approximately dose-proportional and increased with dose across the dose range of 2–30 mg/kg.

All 26 subjects enrolled in the study had evaluable anti-vofatamab antibodies (ATA) samples after treatment, and all tested negative for antibodies to vofatamab.

A total of 10 subjects (38%) had stable disease (SD) as their best clinical response on study. Furthermore, a post-hoc analysis comparing progression-free survival (PFS) of high-dose vofatamab (30 mg/kg) vs. low doses of vofatamab ( $< 30$  mg/kg) showed greater PFS in the high-dose subjects ([Figure 1](#)). This finding was most notable in the evaluable UCC subpopulation, which had a median PFS of 5.7 months for the high-dose group ( $n = 5$ ) compared with a median PFS of 1.7 months in the low-dose group ( $n = 3$ ). Two subjects with UCC were not considered evaluable and were not included in this analysis.

**Figure 1 Progression-Free Survival in Subjects with UCC (Study MFG4991g)**



Note: This data set excludes one subject who received escalating doses of vofatamab (anti-FGFR3), 4 mg/kg up to 30 mg/kg, and a 2<sup>nd</sup> subject dosed at 30 mg/kg who died after Day 4 of the study due to disease progression

^ Subject had a single dose of vofatamab (anti-FGFR3) and dropped out of the study due to thrombocytopenia, possibly related to levofloxacin.

#### 1.2.2.2 Study MFG4809g (Phase 1 Study in Patients with Multiple Myeloma)

Study MFG4809g was an open-label, multicenter, Phase 1 study in subjects with relapsed or refractory t(4;14)-positive multiple myeloma. The safety and PK of escalating doses of vofatamab were evaluated following IV infusion of vofatamab to subjects weekly for 3 weeks (Days 1, 8, and 15 of a 28-day cycle), followed by a single infusion of the same dose on Day 1 of the subsequent cycles. Doses of 1, 2, 4, 8, and 15 mg/kg of vofatamab were evaluated in 14 subjects. The median number of cycles administered was 1.5 and the median number of doses administered was 3.5. The study was terminated early by the Sponsor due to unsatisfactory enrollment.

All subjects had discontinued from the study at the time of study termination for the following reasons: 10 (71.4%) subjects due to disease progression, 3 (21.4%) subjects died (including 2 subjects who died due to disease progression and 1 subject who died due to disease progression with Grade 5 intracranial hemorrhage), and 1 (7.1%) subject due to subject/legal guardian decision to withdraw. All 14 subjects experienced at least one AE. The most common AEs irrespective of study drug attribution were fatigue experienced by 6 (42.9%) subjects; anemia and nausea experienced by 4 (28.6%) subjects each; diarrhea, dyspnea, headache, and thrombocytopenia experienced by 3 (21.4%) subjects each; and confusional state, cough, decreased appetite, hypercalcemia, neutropenia, peripheral edema, platelet count decreased, pyrexia, and urinary tract infection experienced by 2 (14.3%) subjects each. A total of 6 subjects

experienced 9 SAEs between Cycle 1 Day 1 and 90 days after the last administration of vofatamab, including one SAE of Grade 5 intracranial hemorrhage and one SAE of Grade 2 pyrexia, which was deemed related to vofatamab. All other SAEs were considered unrelated to vofatamab. There were no AEs of special interest, and there were no additional AEs of interest identified during the conduct of the study. Furthermore, no events were identified as a DLT and the maximum tolerated dose (MTD) was not reached prior to the Sponsor's decision to stop enrollment.

Given the small sample size, no definitive conclusions regarding anti-tumor activity could be drawn. The best overall response achieved was that of SD, which was reported in 7 of 14 subjects.

Exposure to vofatamab increased with increasing dose. Increases in exposure were non-dose proportional in the lower dose groups of 1 and 2 mg/kg, and approximately dose proportional at all other dose groups (i.e., 4, 8, and 15 mg/kg). FGFR3 levels did not appreciably change upon vofatamab treatment, regardless of dose.

#### 1.2.2.3 Study B-701-U21 (Phase 1/2(b) Study in Patients with Stage IV, Locally Advanced or Metastatic Urothelial Cell Carcinoma)

Interim safety and efficacy data from the Phase 1b Cohort 1 of the current study (Study B-701-U21) are available for subjects with locally advanced or metastatic UCC who received vofatamab plus docetaxel, which evaluated the maximum tolerated dose of vofatamab using the 3 + 3 study design described in [Section 3.1.1.1](#). On Day 1 of each 21-day cycle, subjects were treated with a combination regimen consisting of an intravenous (IV) infusion of docetaxel (75 mg/m<sup>2</sup>) followed by an IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) only was given on approximately Day 8 of Cycle 1 only. Dosing with docetaxel and vofatamab continued in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. Of 20 subjects enrolled in Cohort 1 of Phase 1b, 19 subjects were treated (1 subject progressed prior to treatment) and were included in the interim analysis.

Overall, vofatamab combined with standard-dose docetaxel was well tolerated. No protocol defined dose-limiting toxicities (DLT) were observed. A total of 5 subjects experienced 15 treatment-related AEs which led to vofatamab dose interruption or modification. A total of 4 subjects had docetaxel dose reductions and 1 subject discontinued treatment due to AE (due to disseminated intravascular coagulation). As of June 2018, 15 subject's deaths were reported on study, including 11 due to disease progression, 2 due to adverse events (AEs) (of disseminated intravascular coagulation that was considered possibly related to vofatamab and intracranial hemorrhage that was considered unrelated to vofatamab), and 2 due to unknown causes.

Table 2 presents the June 2018 analysis of the AEs in Cohort 1. All 19 subjects (100.0%) experienced at least 1 AE, with 15 subjects (78.9%) experiencing AEs assessed as related to vofatamab. The most frequent AEs ( $\geq 15\%$  of subjects) assessed as related to vofatamab were diarrhea (31.6%), fatigue (21.1%), neutrophil count decreased (21.1%), alopecia (15.8%), and

nausea (15.8%). A total of 13 subjects (68.4%) and 11 subjects (57.9%) experienced serious AEs and Grade  $\geq 3$  AEs, respectively.

**Table 2. B-701-U21: Summary of Adverse Events in Cohort 1**

	<b>Cohort 1 (N = 19)</b>
Treatment-Emergent Adverse Events (TEAEs)	
Any TEAEs	10 (100.0)
Vofatamab-Related TEAEs	15 (78.9)
Serious TEAEs	
Any Serious TEAEs	11 (57.9)
Vofatamab-Related Serious TEAEs	4 (21.1)
Grade 3/4/5 TEAEs	
Any Grade 3/4/5 TEAEs	13 (68.4)
Grade 5	
Disseminated intravascular coagulation	1 (5.3)
Grade 4	
Neutrophil count decreased	4 (21.1)
Thrombocytopenia	1 (5.3)
Grade 3	
Fatigue	3 (15.8)
White blood cell count decreased	3 (15.8)
Asthenia	1 (5.3)
Clostridium difficile infection	1 (5.3)
Colitis	1 (5.3)
Diarrhea	1 (5.3)
Hyponatremia	1 (5.3)
Lymphocyte count decreased	1 (5.3)

Percentage is calculated using the number of subjects in the column heading as the denominator.

Treatment-emergent adverse events (TEAEs) are defined as AEs that start on or after the first administration of study drug (vofatamab or docetaxel).

Source: Tables 14.3.1.1 and 14.3.1.14; run date: 25Jun2018; data cut-off date: 22Jun2018

A total of 3 subjects (15.8%) had either complete response (5.3%) or partial response (10.5%) as their best clinical response on study. Subjects with FGFR3 mutation or fusions experienced prolonged progression-free survival and the median survival was not reached after 20 months of follow up. Table 3 presents the disease control rate, progression-free survival, and overall

survival for these subjects overall and for subjects with and without FGFR3 gene mutation or fusion.

**Table 3. B-701-U21: Summary of Best Overall Response, Disease Control Rate, Progression-Free Survival, and Overall Survival in Cohort 1**

	<b>Total (N = 19)</b>	<b>Wild Type (N = 13)</b>	<b>FGFR3 Mut/Fus (N = 6)</b>
Best Response of CR or PR	1 CR, 2 PR	1 PR	1 CR, 1 PR
Median Disease control rate, % (95% CI)	63.2 (39.2, 74.5)	53.8 (25.1, 80.8)	83.3 (35.9, 99.6)
Median Progression-free survival, months (95% CI)	3.25 (1.9, 5.2)	2.37 (1.6, 3.7)	6.56 (1.9, 17.3)
Median Overall survival, months (95% CI)	6.87 (4.01, 11.30)	5.32 (3.25, 7.3)	Not Reached at 20 mo follow-up

*CR = complete response; PR = partial response*

*Bellmunt J ASCO Poster 2018. Data cut-off date: 18April2018*



## **2 OBJECTIVES**

### **2.1 Phase 1b (Cohort 1)**

#### **2.1.1 *Primary Objective***

- To determine an acceptable maximum tolerated dose (MTD) of vofatamab plus docetaxel in subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy.

### **2.2 Phase 2 (Cohorts 2 and 3)**

#### **2.2.1 *Primary Objective***

- To evaluate the initial safety and efficacy of vofatamab in combination with docetaxel and vofatamab monotherapy in advanced UCC with FGFR3 genomic aberrations.

### **2.3 Phase 2b Monotherapy Expansion and Randomized Phase**

#### **2.3.1 *Phase 2b Monotherapy Expansion Primary Objective***

- To evaluate the efficacy of vofatamab in the treatment of subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy, as measured by progression-free survival (PFS).

#### **2.3.2 *Secondary Objectives***

- To evaluate overall survival (OS) of vofatamab in the treatment of subjects with UCC.
- To evaluate the efficacy of vofatamab in the treatment of subjects with UCC as measured by objective response rate (ORR), disease control rate (DCR), duration of objective response (DOR), time to response (TTR), and quality of life (QOL).
- To evaluate the safety and tolerability of vofatamab in the treatment of subjects with UCC as measured by anti-vofatamab antibodies (ATA), adverse events (AEs), physical examination, laboratory, and other clinically relevant results.

#### **2.3.3 *Exploratory Objective***

- To evaluate the pharmacokinetics (PK) of vofatamab in advanced UCC

### **2.4 Phase 2b Randomized Phase**

#### **2.4.1 *Primary Objective***

- To evaluate the efficacy of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with Stage IV, locally advanced or metastatic UCC who have

relapsed after, or are refractory to at least one prior line of chemotherapy which has not included a taxane, as measured by progression-free survival (PFS).

#### **2.4.2            *Secondary Objectives***

- To evaluate overall survival (OS) of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with UCC.
- To evaluate the efficacy of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with UCC as measured by objective response rate (ORR), disease control rate (DCR), duration of objective response (DOR), time to response (TTR), and quality of life (QOL).
- To evaluate the safety and tolerability of vofatamab plus docetaxel compared with placebo plus docetaxel in the treatment of subjects with UCC as measured by ATAs, adverse events (AEs), physical examination, laboratory, and other clinically relevant results.

#### **2.4.3            *Exploratory Objectives***

- To study the association between the level of FGFR3 expression, the presence of FGFR3 mutations or fusions, as well as other potential biomarkers (e.g., genetic alterations in other cancer-related genes), in primary tumors or metastases, with efficacy and/or adverse event (AE) outcomes.
- To evaluate the pharmacokinetics (PK) of vofatamab monotherapy and vofatamab in combination with docetaxel in advanced UCC.

### 3 STUDY DESIGN

#### 3.1 Overall Study Design

This is a Phase 1/2(b), sequential, dose escalation, open-label and randomized, expansion multicenter, efficacy and safety study of vofatamab alone or in combination with docetaxel in subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy.

This study is divided into 3 phases: Phase 1b (Cohort 1), Phase 2 (Cohorts 2 and 3) and Phase 2b Phase 2b Monotherapy Expansion and Randomized Phase).

##### 3.1.1 *Phase 1b*

The clinical trial will commence with an open-label dose escalation Phase 1b. Phase 1b consists of Cohort 1

- Cohort 1: Approximately 20 subjects with Stage IV, locally advanced or metastatic UCC who have relapsed after, or are refractory to at least one prior line of chemotherapy which has not included a taxane. All subjects in this cohort will receive both vofatamab plus docetaxel.

##### 3.1.1.1 Cohort 1 of the Phase 1b

Cohort 1 of the study will utilize the following 3 + 3 design:

Initially, one subject will be enrolled in Cohort 1. On Day 1 of Cycle 1, the initial subject in this cohort will be treated with a combination regimen consisting of an IV infusion of docetaxel (75 mg/m<sup>2</sup>) followed by an IV infusion of vofatamab (25 mg/kg). On Day 8 of Cycle 1, the subject will be treated with an IV infusion of vofatamab (25 mg/kg) alone. If the subject experiences a DLT during the DLT observation period (defined as the first 21-day cycle), then additional subjects will be enrolled at the same dose until 6 subjects are enrolled or until  $\geq 2$  subjects have experienced DLTs. If no DLT is observed through Day 21, an additional 2 subjects will be treated, on different days, with the same regimen. If a DLT is observed in 1 of the 3 subjects during the DLT observation period, then additional subjects will be enrolled until at least 6 subjects are enrolled or until  $\geq 2$  subjects have experienced DLT (i.e., with docetaxel 75 mg/m<sup>2</sup> and vofatamab 25 mg/kg). If 0 of 3 subjects or  $\leq 1$  of 6 subjects experience a DLT, additional subjects will be enrolled at that dose so that a total of 20 subjects will be treated in Cohort 1. If at any time,  $\geq 2$  of 6 subjects experience a DLT, the dosing regimen will be modified, by either reducing the dose of vofatamab to 20 mg/kg and/or reducing the dose of docetaxel to 55 mg/m<sup>2</sup>. The dose modification decision will be made based upon the nature of the DLT, e.g., if it is clearly related to one or the other drug, or upon discussion with the participating principal investigators (see [Section 5.1.2](#) for details). A new set of 3 to 6 subjects will be enrolled and treated with the modified dose of vofatamab and/or docetaxel. If at any time, a dose of vofatamab of 20 or 25 mg/kg or a dose of docetaxel of at least 55 mg/m<sup>2</sup> are deemed not tolerable (i.e.,  $\geq 2$  of 6 subjects at the same dose level who have experienced DLTs), enrollment will cease and the study will be stopped until further analysis of the combination regimen can be

performed. Should a subject discontinue dosing with docetaxel at any time during the study, dosing with vofatamab will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

### **3.1.2 Phase 2**

Phase 2 of the study is divided in the following 2 cohorts:

- Cohort 2: Up to 20 subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy which has not included a taxane. All subjects in this cohort will receive both vofatamab plus docetaxel.
- Cohort 3: Up to 20 subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy. All subjects in this cohort will receive vofatamab only.

#### **3.1.2.1 Cohort 2 in Phase 2**

Enrollment in Cohort 2 will commence after the 16th subject is enrolled in Cohort 1 of the Phase 1b. On Day 1 of each 21-day cycle, subjects in Cohort 2 will be treated with a combination regimen consisting of an intravenous (IV) infusion of docetaxel (75 mg/m<sup>2</sup>) followed by an IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) only will be given on approximately Day 8 of Cycle 1 only. Dosing with docetaxel and vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. Should a subject discontinue dosing with docetaxel at any time during the study, dosing with vofatamab will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

#### **3.1.2.2 Cohort 3 in Phase 2**

Enrollment in Cohort 3 will commence after the 16<sup>th</sup> subject is enrolled in Cohort 1 of the Phase 1b. On Day 1 of each 21-day cycle, subjects in Cohort 3 will receive one IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) will be given on approximately Day 8 of Cycle 1 only. Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

### **3.1.3 Phase 2b**

#### **3.1.3.1 Phase 2b Monotherapy Expansion**

Enrollment to the Phase 2b Monotherapy Expansion will commence once Phase 2 has completed enrollment. The Phase 2b Monotherapy Expansion will enroll up to 80 subjects with Stage IV,

locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy. (If a checkpoint inhibitor is not an approved or available therapy for UCC, then this criterion does not apply).

On Day 1 of each 21-day cycle, subjects in the Phase 2b Monotherapy Expansion will receive one IV infusion of vofatamab (25 mg/kg). An additional dose of vofatamab (25 mg/kg) will be given on approximately Day 8 of Cycle 1 only. Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

#### 3.1.3.1.1 Pharmacokinetic Sub-Study

Up to 10 subjects at designated centers in Phase 2b Monotherapy Expansion ([Appendix 8](#)) who provide separate informed consent will participate in a PK Sub-study and will have intensive PK sample collection (samples obtained before and 30 minutes post-dosing) performed on Day 1 of Cycles 1, 2, 3, 5, 6, 10, and end of treatment following the initiation of vofatamab dosing. In addition, for Cycle 1, samples will be collected on Day 2 and 4, and on Day 8 before and 30 minutes post-dosing. In Cycle 5, samples will be collected on Day 2, Day 8, Day 15, and Day 21.

#### 3.1.3.2 Phase 2b Randomized Phase

Enrollment to Randomized Phase in Phase 2b will commence after a review of the safety and efficacy data observed in Cohort 2 of Phase 2. The review will be conducted by the Sponsor and the Safety Oversight Committee (SOC) once the last subject in Cohort 2 of Phase 2 has completed at least 6 months of follow-up on study, to evaluate the potential safety and efficacy benefit of the addition of vofatamab to docetaxel chemotherapy. Subjects with Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy which has not included a taxane will be enrolled. (If a checkpoint inhibitor is not an approved or available therapy for UCC, then this criterion does not apply.)

Subjects will be randomly assigned in a 2:1 ratio to receive therapy with either vofatamab plus docetaxel (Arm A, experimental arm) or placebo plus docetaxel (Arm B, control arm). Random assignment will be stratified by visceral metastasis (presence vs. absence).

**Arm A (vofatamab plus docetaxel):** On Day 1 of each 21-day cycle, subjects will receive one IV infusion of docetaxel followed by one IV infusion of vofatamab, using the MTD identified in Cohort 1. An additional dose of vofatamab, (without docetaxel; and at the dose identified in Cohort 1) will be given on approximately Day 8 of Cycle 1 only.

**Arm B (placebo plus docetaxel):** On Day 1 of each 21-day cycle, subjects will receive one IV infusion of docetaxel, using the MTD identified in Cohort 1, followed by one IV infusion of placebo. An additional dose of placebo (without docetaxel) will be given on approximately Day 8 of Cycle 1 only.

Crossover from Arm A to Arm B and vice versa will not be allowed.

Phase 2b Randomized Phase will enroll approximately 160 subjects.

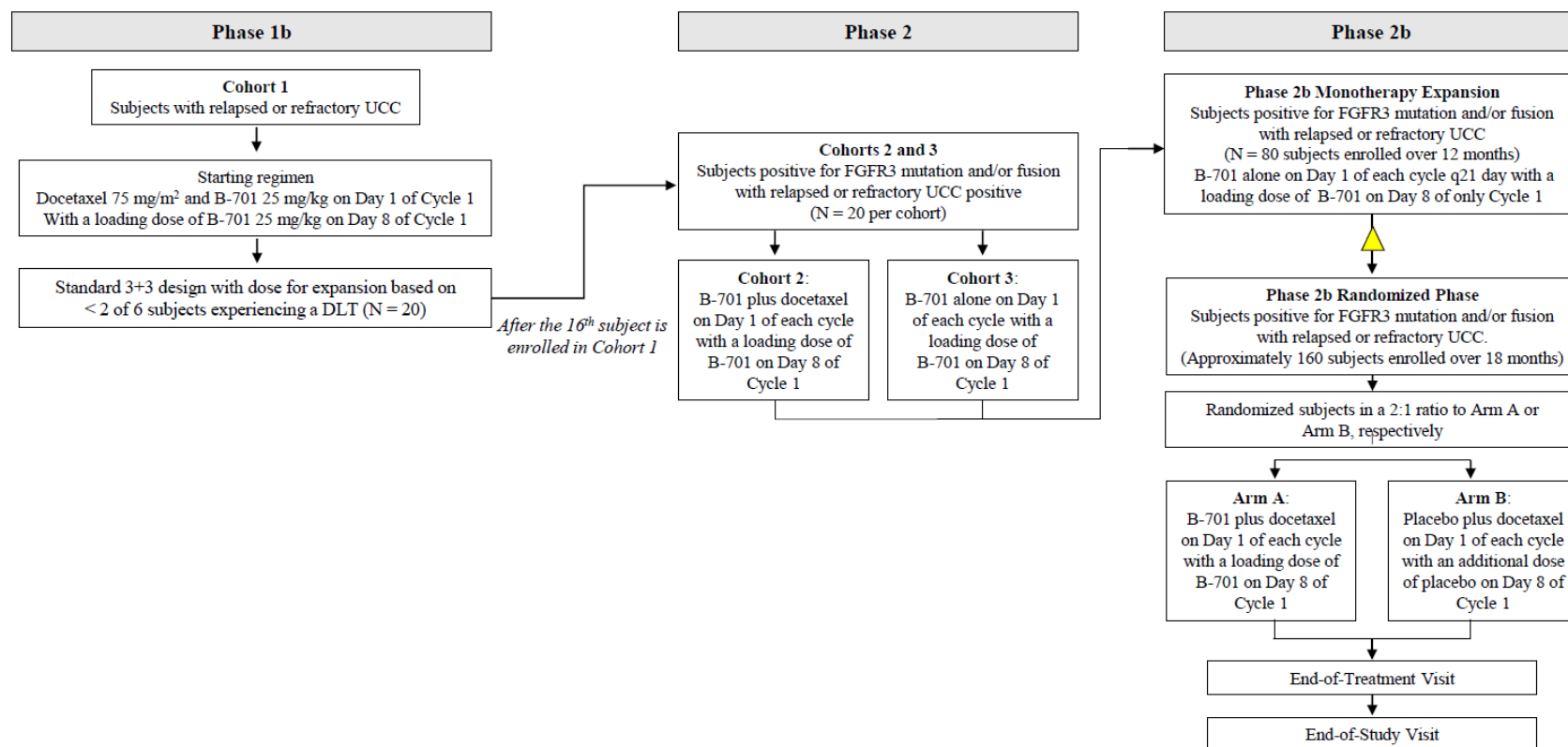
### **3.1.4            *Phase 1b, Phase 2, and Phase 2b Assessments***

Clinical response assessments will be performed every 9 weeks  $\pm$  1 week (i.e., every third cycle beginning at the Screening visit) until disease progression or lack of tolerability. Response assessments will be reported by the investigator and reviewed by the Medical Monitor.

Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. Docetaxel treatment beyond 12 cycles of therapy may be considered at the discretion of the treating investigator and Medical Monitor, and after a careful assessment and discussion of risk versus benefit with the subject.

The study design is summarized in [Figure 2](#).

**Figure 2 Study Design**



▲ Enrollment to Phase 2b Randomized Phase will commence after a review of the safety and efficacy data observed in Cohort 2 of Phase 2.

**Abbreviations:** DLT = dose limiting toxicity; q21 = every 21 days; UCC = urothelial cell carcinoma

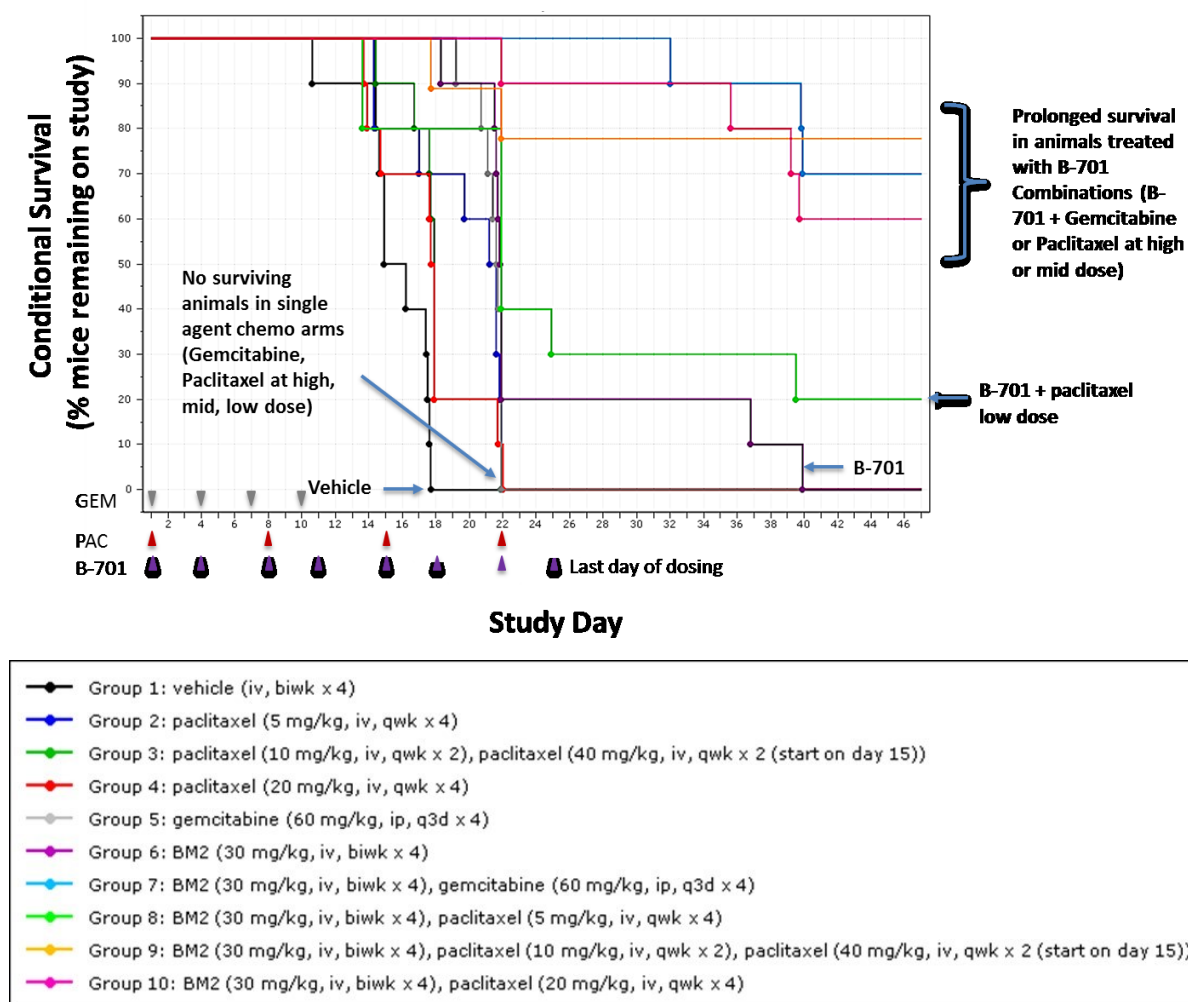
**Note:** Should a subject discontinue dosing with docetaxel at any time during the study, dosing with B-701 will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

## 3.2 Discussion of Study Design

### 3.2.1 Selection of Dose and Dosing Schedule

The combination regimen of vofatamab plus docetaxel was selected based on preclinical data, which demonstrated that the combination of vofatamab plus a taxane was highly effective in suppressing tumor growth in a mouse xenograft model of bladder cancer (Figure 3). Similar to previously observed results with gemcitabine, the combination of vofatamab plus paclitaxel, at doses of either 10 mg/kg qw × 2 / 40mg/kg qw × 2 or 20 mg/kg qw × 4, resulted in greater tumor suppression than either agent alone (Figure 3). These data support the clinical testing of vofatamab in combination with a taxane, such as docetaxel.

**Figure 3 Tumor Suppression Following Vofatamab Treatment in a Bladder Cancer Xenograft Model (UMUC-1)**



The dosing regimen of vofatamab at 25 mg/kg every 21 days was selected since it is estimated to provide a steady-state area under the concentration curve (AUC) comparable to



30 mg/kg every 28 days, a dose and regimen that was administered and found to be generally safe and well-tolerated in the completed Phase 1 study in advanced solid tumors. From an efficacy perspective, this dose is anticipated to be sufficient based on extrapolation from preclinical PK/pharmacodynamic analyses.

Lower and higher dose levels than 25 mg/kg every 21 days are not tested in this study because:

1. Dose levels lower than 25 mg/kg every 21 days are predicted to provide less efficacy based on extrapolation from preclinical PK/pharmacodynamic analyses. Given the excellent safety and tolerability of vofatamab at 30 mg/kg every 28 days from the solid tumor Phase 1 study, and given the severity of the target disease of advanced, relapsed or refractory UCC, the potential benefit-risk of a lower dose level is deemed less favorable than 25 mg/kg every 21 days and thus will not be tested in this study.
2. The MTD was not established in the solid tumor Phase 1 study and thus higher doses of vofatamab could theoretically be explored. However, dose levels higher than 25 mg/kg every 21 days would be an extraordinary amount of a monoclonal antibody to be administered, and is not likely to provide additional benefit-risk. Thus, a dose level higher than 25 mg/kg every 21 days will not be tested in this study.

Similar to the completed Phase 1 study, to achieve steady state exposure and potential clinical benefit as quickly as possible, an additional loading dose of 25 mg/kg of vofatamab will be administered on approximately Day 8 of Cycle 1 only. From a safety perspective, the loading doses of 25 mg/kg on Days 1 and 8 are slightly lower than the loading doses of 30 mg/kg on Days 1 and 8 that were administered in the previous Phase 1 advanced solid tumor study.

The following information provides further details:

- Preclinical studies in mice produced data from which it was estimated that a steady-state AUC of 850 day  $\times$   $\mu$ g/mL on a weekly basis, or 3400 day  $\times$   $\mu$ g/mL with administration every 4 weeks was needed for efficacy. Using compartmental PK analysis, it was determined that IV administration of 20 mg/kg and 30 mg/kg of vofatamab every 21 days are expected to have steady-state AUC of 3529 day  $\times$   $\mu$ g/mL and 5293 day  $\times$   $\mu$ g/mL, respectively. Thus, 25 mg/kg every 21 days is predicted to provide adequate doses for efficacy and that lower doses would be inadequate.
- Results from Study MFG4991g demonstrated the following:
  - Administration of vofatamab across the dose range of 2 to 30 mg/kg every 28-days was well-tolerated in subjects with advanced solid tumors.
  - Serum exposure of vofatamab was approximately dose-proportional and increased with dose across the dose range of 2–30 mg/kg tested.
  - Six of the 10 subjects who had SD as their best clinical response on study were treated with 30 mg/kg vofatamab every 28-days.

- Based on a population PK analysis of the data from Study MFG4991g, the post-hoc estimate of steady-state AUC for 30 mg/kg every 28-days was  $5021 \text{ day} \times \mu\text{g/mL}$ .

Studies MFG4991g and MFG4809g had loading doses in Cycle 1. In Study MFG4809g, doses were given on Days 1, 8 and 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle. In Study MFG4991g, doses were given on Days 1 and 8 in Cycle 1, and then on Day 1 of each subsequent 28-day.

### **3.2.2 Selection of Control**

#### **3.2.2.1 Docetaxel**

To date, several Food and Drug Administration (FDA)-approved second-line therapies for the treatment of bladder cancer exist. However, the National Comprehensive Cancer Network Guidelines on Bladder Cancer (2014) recommend the use of docetaxel, paclitaxel, or gemcitabine as control agents in bladder cancer trials ([NCCN 2014](#)). Since gemcitabine is typically a first-line treatment, second-line treatment usually consists of a taxane (e.g., docetaxel or paclitaxel [[Galsky 2005](#); [McCaffrey 1997](#); [Papamichael 1997](#); [Vaughn 1999](#)]). In a poll of 11 key opinion leaders, a taxane was the most widely used second-line therapy, and a majority favored docetaxel 75 mg/m<sup>2</sup> every 21 days over paclitaxel due to a better tolerability profile.

#### **3.2.2.2 Placebo**

The use of placebo will enable Randomized Phase in Phase 2b of the study to be double-blind, which is necessary since the primary endpoint, PFS, may be influenced if subjects or investigators are unblinded to the treatment assignment. Knowledge of the treatment assignment could: (1) result in different patterns of requests for unscheduled computerized tomography (CT) scans, which could bias the PFS results; and (2) result in more drop-outs of subjects in the placebo arm, which could also bias PFS results due to differential drop-out patterns between the two treatment arms.

### **3.2.3 Selection of Study Population**

This study will be conducted in subjects with Stage IV, locally advanced or metastatic relapsed/refractory UCC (Cohort 1) and Stage IV, locally advanced or metastatic UCC positive for FGFR3 mutation and/or fusion; who are ineligible for or who have relapsed after, or are refractory to an immune checkpoint inhibitor and at least one prior line of chemotherapy (Cohorts 2 and 3 of Phase 2, and Phase 2b Monotherapy Expansion and Randomized Phase of Phase 2b).

Preclinical data indicate that antibody targeting of FGFR3 may be a valuable clinical strategy in the treatment of UCC. In addition, an analysis of metastatic tumor tissue in UCC subjects demonstrates that approximately 74% of subjects with UCC have high FGFR3 expression ([Du 2011](#)). Results from Study MFG4991g, in subjects with advanced solid tumors, also showed that the greatest increase in PFS following treatment with vofatamab, was in subjects with UCC (see [Section 1.2.2.1](#)). Thus, this population was chosen on the basis of high unmet

need, together with preclinical and clinical evidence that vofatamab has promising therapeutic potential in this indication.

#### 3.2.3.1 Rationale for FGFR3 Expression Criterion

Because vofatamab is a highly selective agent, targeting the FGFR3 receptor, only those subjects who express the target are likely to benefit from treatment. Therefore, subjects in Cohort 1 of the Phase 1b will be retrospectively tested using an immunohistochemistry (IHC) assay for FGFR3, and only subjects with confirmed FGFR3 mutation and/or fusion will be enrolled in Cohorts 2 and 3 of Phase 2 and Phase 2b Monotherapy Expansion and Randomized Phase of Phase 2b. Additional analyses will be performed to determine whether a threshold level of FGFR3 expression is associated with vofatamab efficacy.

#### 3.2.4 *Duration of Subject Participation*

Subjects will participate in the study for approximately 36 months, including a 28-day screening period, 21-day cycles of treatment, and follow-up to monitor survival.

#### 3.2.4.1 Definition of End of Study

The end of the study (i.e., the last visit) will occur when the last subject completes the End of Study visit.

## **4 STUDY POPULATION AND WITHDRAWAL**

### **4.1 Inclusion Criteria**

Individuals eligible to participate in this study must meet all of the following criteria listed in [Sections 4.1.1 through 4.1.3](#).

#### **4.1.1 Disease Specific Inclusion Criteria**

1. Stage IV, locally advanced or metastatic (T4b, any N; or any T, N2-3) urothelial bladder cancer or TCC arising in another location of the urinary tract, including urethra, ureter, and renal pelvis
2. Histological or cytological diagnosis of UCC. Mixed histologies are permitted as long as TCC is the major component (i.e., > 50% of the pathologic specimen). Pure or predominant squamous cell carcinomas or adenocarcinomas are not permitted
3. Relapsed after or are refractory to at least one prior line of chemotherapy which has not included a taxane (with the exception of Cohort 3 of Phase 2 and Phase 2b Monotherapy Expansion of Phase 2b which will allow the enrollment of subjects with prior treatment with a taxane)
4. Subjects must have received at least one prior chemotherapeutic regimen (at least one cycle each) for advanced or metastatic/recurrent disease, of which at least one regimen included a platinum agent. If a platinum agent is contraindicated for a subject (e.g., due to pre-existing renal impairment such as creatinine clearance < 60 mL/min, myelosuppression, hearing impairment, or history of allergic reaction to platinum-containing compounds), the prior regimen(s) need not have included a platinum agent. Reason for platinum contraindication will be collected in the eCRFs
5. Prior neoadjuvant or adjuvant chemotherapy (without a taxane, except Cohort 3 of Phase 2 and Phase 2b Monotherapy Expansion, which will allow the enrollment of subjects with prior treatment with a taxane) is permitted and will not be counted as first-line chemotherapy, as long as the subject has not progressed within 12 months of the last dose. However, if the patient progressed within 12 months of the last dose of prior neoadjuvant or adjuvant chemotherapy, then this regimen of neoadjuvant or adjuvant chemotherapy will be counted as first-line chemotherapy
6. Measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1; see [Appendix 3](#)). If possible, sites of measurable disease should not be within a previously irradiated site. However, if all sites of measurable disease have been irradiated, at least one site must have demonstrated growth after irradiation
7. Subjects must be anticipated to have a PFS of at least 4 weeks from the time of randomization (i.e., tumor progression per RECIST v1.1 is not anticipated within the first 4 weeks after randomization)

#### **4.1.2 Phase 2 and Phase 2b Specific Inclusion Criteria**

1. Tumor shown to have at least one of the following FGFR3 mutations: R248C, S249C, G370/2C, S371/3C, Y373/5C, G380/82R, F384/6L, K650/2X (X=E,T or M) or FGFR3-TACC3 fusion, as shown by tests performed by a CAP or CLIA certified laboratory (or equivalent outside of the US) such as Foundation Medicine, Ashion Analytics, or Paradigm Diagnostics on samples that were obtained at or after the time when the subject was found to have muscle invasive disease or high grade papillary non-muscle invasive disease. In the absence of pre-existing genetic test results, subjects can submit archival tissue (obtained at or after the time subject was found to have muscle invasive disease) for genetic testing. When such archival tissue is not immediately available, a blood sample may be submitted for initial determination of FGFR3 mutation and/or fusion status. In all cases, subsequent to subject enrollment, previous test results that were not provided by Foundation Medicine will be verified using archival tissue (if not available for Randomized Phase, a core biopsy may be obtained). Blood samples will be obtained on Cycle 1 Day 1 to verify results observed in archival tissues or core biopsies.
2. Relapsed after or are refractory to an immune checkpoint inhibitor (such as atezolizumab, pembrolizumab, nivolumab, avelumab, or durvalumab). This inclusion criterion does not apply if the checkpoint inhibitor is contraindicated. Reason for checkpoint inhibitor contraindication will be collected in the eCRFs. If a checkpoint inhibitor is not an approved or available therapy for UCC, then this inclusion criterion does not apply.

#### **4.1.3 General Inclusion Criteria**

1. Signed informed consent form, including:
  - a. Consent to provide tumor tissue and blood samples for genetic testing
  - b. Consent to provide metastatic tumor tissue during the study, if available, or at autopsy for testing of FGFR3 status, as well as other potential biomarkers
  - c. Consent to provide survival information after completion of study drug dosing
2. For Cohort 1, archival tumor samples must be available for retrospective sequencing of cancer-related genes, including FGFR3, by NGS. For Cohorts 2 and 3 of Phase 2 and all subjects in Phase 2b Monotherapy Expansion and Randomized Phase, subjects must be confirmed to have a FGFR3 genomic alteration at the time of documentation of advanced disease. Available tissue that was obtained at or after the time the subject was found to have muscle invasive disease and is of suitable quality and quantity (as outlined in the Sponsor's Laboratory Instructions) should be used to assess the FGFR3 status by genetic testing. A blood sample to assess the FGFR3 status of circulating tumor DNA by genetic sequencing must also be provided (described in [Section 6.2.2](#)). In case no archival tissue sample is available or tissue testing was not informative, a blood sample to assess the FGFR3 status by circulating tumor DNA (ctDNA) can be submitted and if positive will be considered adequate for inclusion. For subjects participating in Phase 2b Monotherapy Expansion and Randomized Phase, if suitable archival tissue is unavailable and ctDNA is not informative, then a

core biopsy of tumor tissue (metastatic or primary from any anatomical location except the bone, lung or brain) can be obtained to determine FGFR3 status.

3. Age  $\geq 18$  years ( $\geq 20$  years in Taiwan)
4. Life expectancy  $\geq 12$  weeks
5. Presence of less than 3 of the following 3 poor prognostic factors:
  - a. Eastern Cooperative Oncology Group (ECOG) performance status (PS)  $\geq 1$ ,
  - b. hemoglobin  $<10$  g/dL, and
  - c. presence of liver metastasis(Note: presence of all 3 poor prognostic factors correlates with rapid progression and a median survival of 1.7 months (Bellmunt 2010; see also Figure 1))
6. ECOG PS of 0 or 1 (see [Appendix 1](#))
7. Adequate hematologic and end organ function defined by the following laboratory results obtained within two weeks prior to the first dose of study treatment:
  - a. Absolute neutrophil count  $\geq 1500/\mu\text{L}$
  - b. Platelet count  $\geq 100,000/\mu\text{L}$
  - c. Hemoglobin  $\geq 9.0$  g/dL without transfusion
  - d. Albumin  $\geq 2.5$  g/dL
  - e. Total bilirubin  $\leq$  upper limit of normal (ULN) (without exception, as stated in the docetaxel package insert)
  - f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)  $\leq 2.5 \times \text{ULN}$ , with the following exceptions:
    - Subjects with documented bone metastases:  $\text{ALP} \leq 5 \times \text{ULN}$
    - Note: Subjects with AST and/or ALT  $> 1.5 \times \text{ULN}$  concomitant with alkaline phosphatase  $> 2.5 \times \text{ULN}$  will not be allowed to enroll, regardless of presence of liver or bone metastases, as stated in the docetaxel package insert
  - g. Creatinine clearance  $\geq 30$  mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$
  - h. Prothrombin time/international normalized ratio (PT/INR) and partial thromboplastin time (PTT) must be  $\leq 1.5 \times \text{ULN}$
8. Willingness to avoid pregnancy or fathering children based on the criteria below:
  - a. Women of non-childbearing potential (i.e., surgically sterile with a hysterectomy and/or bilateral oophorectomy OR chemically sterile OR  $\geq 12$  months of amenorrhea in the absence of chemotherapy, anti-estrogens, or ovarian suppression). Women of non-childbearing potential need not undergo pregnancy testing

- b. Women of childbearing potential who have a negative urine or serum pregnancy test at Screening and before the first dose of study drug on Cycle 1, Day 1, and who agree to take appropriate precautions to avoid pregnancy (with approximately 99% certainty) from Screening through 90 days after the last dose of study drug. Permitted methods of contraception that are approximately 99% effective in preventing pregnancy are described in [Appendix 6](#), should be communicated to the subject, and the subject's understanding confirmed
  - c. Men who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from Screening through 90 days after the last dose of study drug. Permitted methods of contraception that are approximately 99% effective in preventing pregnancy are described in [Appendix 6](#), should be communicated to the subject, and the subject's understanding confirmed
9. Negative urine or serum pregnancy test within 3 days prior to randomization in women of childbearing potential
10. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule (such conditions should be discussed with the subject before study entry)

#### **4.2 Exclusion Criteria**

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

- 1. Prior use of any other investigational drug (i.e., monoclonal antibody or experimental therapy) within 2 weeks before Cycle 1, Day 1
- 2. Palliative radiotherapy within 2 weeks prior to Cycle 1, Day 1
- 3. Prior anti-cancer therapy (e.g. biologic or other targeted therapy, chemotherapy or hormonal therapy) within 2 weeks prior to Cycle 1, Day 1
  - a. A washout of less than 14 days may be allowed after discussion with the Medical Monitor, provided that the subject has recovered from any clinically relevant toxicity (Exception: participants with neuropathy of Grade 1 will be allowed study entry)
  - b. Clinical AEs, except for alopecia, from any previous treatments must have resolved to  $\leq$  Grade 1
  - c. Laboratory AEs from any previous treatments must have resolved to  $\leq$  Grade 1 or to within 10% of baseline prior to Cycle 1, Day 1
- 4. Prior treatment with an inhibitor that is targeted primarily to FGFRs
- 5. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins)
- 6. Inability to be pre-medicated with a corticosteroid when treated with docetaxel
- 7. Evidence of significant, uncontrolled concomitant diseases which could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association (NYHA) Class III or IV

- cardiac disease (see [Appendix 2](#)), myocardial infarction or stroke within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
8. History of major bleeding (requiring a blood transfusion  $\geq 2$  units) not related to a tumor within the past 12 months
  9. History of clinically significant coagulation or platelet disorder in the past 12 months
  10. Currently receiving anticoagulation treatment
  11. Incomplete healing from wounds from prior surgery; wound is larger than 2 cm in length 28 days prior to randomization
  12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at screening. Any major episode of infection requiring treatment with IV antibiotics or hospitalization must be resolved (including the completion of the course of antibiotics) prior to Cycle 1, Day 1
  13. History of other malignancy which could affect compliance with the protocol or interpretation of results
  14. Subjects with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are allowed
  15. Subjects with a malignancy that has been treated with curative intent will also be allowed if the malignancy has been in remission without treatment for  $\geq 2$  years prior to Cycle 1, Day 1
  16. Subjects with localized prostate cancer that has been treated with curative intent will be allowed
  17. Presence of positive test results for Hepatitis B (Hepatitis B surface antigen [HBsAg] and/or total Hepatitis B core antibody [anti-HB-c]) or Hepatitis C (Hepatitis C virus [HCV] antibody serology testing)  
  
Subjects positive for anti-HB-c are eligible only if polymerase chain reaction (PCR) is negative for Hepatitis B viral (HBV) deoxyribonucleic acid (DNA)
  18. Known history of human immunodeficiency virus (HIV) seropositive status
  19. Primary central nervous system (CNS) malignancy, or CNS metastases
  20. Pregnancy (positive pregnancy test), lactation or breastfeeding
  21. Inability to comply with study and follow up procedures
  22. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications



### **4.3 Discontinuation Criteria**

#### **4.3.1 *Subject Discontinuation***

Subjects must be withdrawn from the study if they experience disease progression (defined using RECIST v1.1 in [Appendix 3](#)). Subjects may continue vofatamab and/or docetaxel therapy beyond progression based on the clinical judgement of the investigator that the subject is experiencing clinical benefit and with subject re-consent. A written request explaining the clinical benefit and patient assent to continuing treatment should be sent to the medical monitor with a request for consultation. Following consultation and, if needed, discussion with the medical monitor, the subject may continue on treatment as long as they are experiencing clinical benefit until the next scheduled evaluation at which time the case will need to be re-discussed with the medical monitor team.

Subjects may discontinue study drug treatment early (i.e., for reasons other than disease progression) for reasons such as subject/investigator choice or unacceptable toxicity (or DLT). The reasons for early discontinuation of treatment must be documented on the appropriate electronic case report form (eCRF).

Subjects who discontinue study treatment early due to toxicity (or DLT) should continue to be followed for resolution or stabilization of toxicity as scheduled.

Subjects must be withdrawn from the study if they become pregnant.

The investigator has the right to discontinue a subject from the study for any medical condition that the investigator determines may jeopardize the subject's safety if he or she continues in the study, for reasons of noncompliance (e.g., missed doses [ $\geq 2$  doses], visits), or if the investigator determines it is in the best interest of the subject.

The End of Treatment/Early Termination (ET) visit assessments should be performed on subjects who prematurely withdraw from the study during the treatment period. Subjects should be followed for safety outcomes for 30 days following the subject's last dose of study drug or until the subject receives another anti-cancer therapy, whichever occurs first.

##### **4.3.1.1 Subject Replacement**

Subjects who discontinue the study early will not be replaced.

#### **4.3.2 *Study Discontinuation***

BioClin (hereafter referred to as the "Sponsor") has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.

- Data recording is inaccurate or incomplete.

## **5 TREATMENT OF SUBJECTS**

### **5.1 Treatment Regimen**

#### **5.1.1 Premedication**

Premedication with a corticosteroid will be administered according to the site's institutional standard. An acceptable regimen may consist of dexamethasone 8 mg orally, twice-a-day, for 3 days, beginning one day prior to docetaxel infusion. Other premedications, such as anti-emetics or antihistamines, may be prescribed, as needed, based on the investigator's assessment.

#### **5.1.2 Cohort 1 of Phase 1b**

Initially, one subject will be enrolled in Cohort 1. On Day 1 of Cycle 1, the initial subject in this cohort will be treated with a combination regimen consisting of an IV infusion of docetaxel (75 mg/m<sup>2</sup>) followed by an IV infusion of vofatamab (25 mg/kg). On Day 8 of Cycle 1, the subject will be treated with an IV infusion of vofatamab (25 mg/kg) alone. If the subject experiences a DLT during the DLT observation period (defined as the first 21-day cycle), then additional subjects will be enrolled at the same dose until 6 subjects are enrolled or until  $\geq 2$  subjects have experienced DLTs. If no DLT is observed through Day 21, an additional 2 subjects will be treated, on different days, with the same regimen. If a DLT is observed in 1 of the 3 subjects during the DLT observation period, then additional subjects will be enrolled until at least 6 subjects are enrolled or until  $\geq 2$  subjects have experienced DLT (i.e., with docetaxel 75 mg/m<sup>2</sup> and vofatamab (25 mg/kg). If 0 of 3 subjects or  $\leq 1$  of 6 subjects experience a DLT, additional subjects will be enrolled at that dose so that a total of 20 subjects will be treated in Cohort 1 of the Phase 1b. If at any time,  $\geq 2$  subjects experience a DLT, the dosing regimen will be modified, by either reducing the dose of vofatamab to 20 mg/kg and/or reducing the dose of docetaxel to 55 mg/m<sup>2</sup>. The dose modification decision will be made based upon the nature of the DLT, e.g., if it is clearly related (i.e., possibly, probably or definitely related) to one or the other drug, or upon discussion with the participating principal investigators. Please see [Sections 5.1.2.1](#) and [5.1.6.2.1](#) for details on the nature of DLTs.

Briefly, if 2 or more of up to 6 subjects had DLTs that were deemed by the investigators to be possibly, probably or definitely related to vofatamab and definitely not or unlikely related to docetaxel, then only the vofatamab dose level would be reduced while the docetaxel dose level would remain unchanged.

If 2 or more of up to 6 subjects had DLTs that were deemed by the investigators to be possibly, probably or definitely related to docetaxel and definitely not related or unlikely related to vofatamab, then only the docetaxel dose level would be reduced while the vofatamab dose level would remain unchanged.

If 2 or more of up to 6 subjects had DLTs that were considered by investigators to be possibly, probably or definitely related to both vofatamab and docetaxel, then both the docetaxel dose level and vofatamab dose levels would be reduced.

When DLTs are analyzed by investigators as to relatedness to vofatamab or docetaxel, investigators should consider that the following AEs could be considered more likely due to docetaxel than vofatamab (anemia, neuropathy, dysgeusia, dyspnea, constipation, nail disorders, fluid retention, pain, alopecia, skin reactions, and myalgia). The following AEs may be attributed to either docetaxel, vofatamab, or to both, such that, for these AEs, modification of the doses for either or both docetaxel and vofatamab should be considered; allergic or non-allergic infusion reaction (fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, hypotension, hypersensitivity, anaphylaxis, dyspnea, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress), mucositis, thrombocytopenia, neutropenia, leukopenia, infections, hypersensitivity, diarrhea, anorexia, asthenia/fatigue, flushing, pain and headache. All other AEs not listed in the prior paragraph above may also be attributed to either docetaxel, vofatamab, or to both.

After dose modification, a new set of 3 to 6 subjects will be enrolled and treated with the modified dose of vofatamab and/or docetaxel. If at any time, a dose of vofatamab of 20 or 25 mg/kg or a dose of docetaxel of at least 55 mg/m<sup>2</sup> are deemed not tolerable (i.e.,  $\geq 2$  subjects at the same dose level who have experienced DLTs), enrollment will cease and the study will be stopped until further analysis of the combination regimen can be performed. Should a subject discontinue dosing with docetaxel at any time during the study, dosing with vofatamab will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

#### 5.1.2.1 Dose-Limiting Toxicity Evaluation and Follow-Up

A DLT will be defined as any of the following AEs considered by the investigator to be (i.e., possibly, probably or definitely related) related to vofatamab occurring during the DLT assessment window (Cohort 1, Days 1–21 of the Phase 1b). All AEs should be considered to be possibly, probably or definitely related to vofatamab, unless such a relationship clearly can be excluded. All AEs, including DLTs, are to be reported according to instructions in [Section 8.6.1](#) and graded according to the NCI CTCAE, v4.0.

- Grade 3/4 hematologic toxicity deemed to be possibly, probably, or definitely related to vofatamab, meeting the following criteria:
  - Grade 4 neutropenia  $> 5$  days in the absence of fever
  - Grade 3 or 4 neutropenia with fever
  - Any Grade 4 thrombocytopenia
  - Grade 3 thrombocytopenia with hemorrhage
- Grade  $\geq 3$  non-hematologic, except for the following:
  - Grade 3 nausea or vomiting (in the absence of premedication) that resolves to Grade  $\leq 1$  within 72 hours with appropriate supportive therapy
  - Grade 3 diarrhea that resolves to Grade  $\leq 1$  within 72 hours with appropriate supportive therapy

- Grade 3 fatigue that resolves to Grade  $\leq 1$  within 72 hours with appropriate supportive therapy
- Grade 3 elevation of total bilirubin, hepatic transaminases (ALT or AST), or ALP, with the following exceptions:
  - For subjects with Grade 2 hepatic transaminase levels at baseline ( $\leq 5 \times \text{ULN}$ ) as a result of liver metastases, only a hepatic transaminase level  $> 10 \times \text{ULN}$  (NCI CTCAE v4.0 Grade 3 is  $> 5.0$  to  $20.0 \times \text{ULN}$ ) will be considered a DLT
  - For subjects with Grade 2 ALP levels at baseline as a result of liver or bone metastases, only an ALP level  $> 10 \times \text{ULN}$  (NCI CTCAE v4.0 Grade 3 is  $> 5.0$  to  $20.0 \times \text{ULN}$ ) will be considered a DLT
  - Note: Subjects who develop Grade  $\geq 3$  AST or ALT and Grade  $\geq 2$  bilirubin elevation with ALP  $\leq 2 \times \text{ULN}$  (i.e. Hy's Law criteria) will be considered to have DLT, irrespective of baseline LFTs
- Adverse events which prevent the administration of study drug on Cycle 1 Day 8 or which delay, by  $> 2$  weeks, administration of study drug on Cycle 1 Day 8 will be considered DLT

If a subject experiences a DLT, he or she will be treated according to clinical practice. Vofatamab will be withheld until the toxicity resolves to Grade 1 or baseline or, in the case of laboratory abnormalities, returns to Grade 1 or to within 10% of the baseline value within 21 days.

### **5.1.3 Cohort 2 of Phase 2**

On Day 1 of each 21-day cycle, subjects will receive one IV infusion of docetaxel, 75 mg/m<sup>2</sup>, over approximately 60 minutes; followed by one IV infusion of vofatamab, 25 mg/kg. The initial dose of vofatamab will be administered 30 minutes after completion of the docetaxel infusion and will be administered over 90 ( $\pm 15$ ) minutes to well-hydrated subjects. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 ( $\pm 10$ ) minutes, followed by a 30-minute observation period post infusion. An additional dose of study drug (vofatamab 25 mg/kg) will be given on Day 8 of Cycle 1 only.

Dosing with docetaxel and vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. Should a subject discontinue dosing with docetaxel at any time during the study, dosing with vofatamab will continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. The rules for continued dosing are provided in [Section 5.1.6.1](#), and dose modification instructions are provided in [Section 5.1.6.2](#). Additional drug administration details are provided in the Sponsor's Pharmacy Instructions.

### **5.1.4 Cohort 3 of Phase 2**

On Day 1 of each 21-day cycle, subjects will receive one IV infusion of vofatamab, 25 mg/kg. The initial dose of vofatamab will be administered over 90 ( $\pm 15$ ) minutes to

well hydrated subjects. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion. An additional dose of study drug (vofatamab 25 mg/kg) will be given on Day 8 of Cycle 1 only.

Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. The rules for continued dosing are provided in [Section 5.1.6.1](#), and dose modification instructions are provided in [Section 5.1.6.2](#). Additional drug administration details are provided in the Sponsor's Pharmacy Instructions.

### **5.1.5 Phase 2b Monotherapy Expansion**

On Day 1 of each 21-day cycle, subjects will receive one IV infusion of vofatamab, 25 mg/kg. The initial dose of vofatamab will be administered over 90 ( $\pm$  15) minutes to well-hydrated subjects. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion. An additional dose of study drug (vofatamab 25 mg/kg) will be given on Day 8 of Cycle 1 only.

Dosing of vofatamab will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination. The rules for continued dosing are provided in [Section 5.1.6.1](#), and dose modification instructions are provided in [Section 5.1.6.2](#). Additional drug administration details are provided in the Sponsor's Pharmacy Instructions.

### **5.1.6 Phase 2b Randomized Phase**

On Day 1 of each 21-day cycle, subjects will receive one IV infusion of docetaxel over approximately 60 minutes, followed by one IV infusion of study drug (vofatamab in Arm A or placebo in Arm B), using the MTD identified in Cohort 1 of the Phase 1b in [Section 5.1.2](#). The initial dose of study drug (vofatamab or placebo) will be administered 30 minutes after completion of the docetaxel infusion and will be administered over 90 ( $\pm$  15) minutes to well-hydrated subjects. If prior infusions have been well-tolerated, subsequent doses of study drug (vofatamab or placebo) may be administered over 30 ( $\pm$  10) minutes, followed by a 30-minute observation period post infusion. An additional dose of study drug (vofatamab 25 mg/kg or placebo) will be given on Day 8 of Cycle 1 only.

Dosing will continue in each subject until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or termination. The rules for continued dosing are provided in [Section 5.1.6.1](#), and dose modification instructions are provided in [Section 5.1.6.2](#). Additional drug administration details are provided in the Sponsor's Pharmacy Instructions.

#### 5.1.6.1 Guidelines for Continued Dosing

To be eligible to receive additional infusions of study drug, subjects must meet the following criteria for ongoing clinical benefit and acceptable toxicity:

- Ongoing clinical benefit: Subjects must have no signs or symptoms of progressive disease (PD). Subjects will be clinically assessed for disease progression on Day 1 of each cycle. Subjects with PD (as defined by RECIST v1.1 in [Appendix 3](#)), will be ineligible to receive further treatment with study drug.
- Acceptable toxicity: All study drug-related (i.e., possibly, probably or definitely related) AEs from prior infusions must have decreased to Grade 1 or baseline grade on or before the day of the next infusion. Exceptions on the basis of ongoing clinical benefit may be allowed after a careful assessment and discussion of risk versus benefit with the subject by the investigator and approval from the Medical Monitor, with the option of dosing study drug (vofatamab or placebo) at the full dose of 25 mg/kg or reducing the dose of study drug (vofatamab or placebo) to 20 mg/kg. In addition, delay of therapy due to toxicities not attributed to study drug (i.e., definitely not related or unlikely related) may not require discontinuation and must be discussed with the Medical Monitor.

#### 5.1.6.2 Dose Modification

The following AEs are more likely to be attributed to docetaxel and not to vofatamab such that, for these AEs, modification of the dose of docetaxel and not vofatamab should be considered: anemia, neuropathy, dysgeusia, constipation, nail disorders, fluid retention, alopecia, skin reactions, and myalgia.

The following AEs may be attributed to either docetaxel or vofatamab or both such that, for these AEs, modification of the dose of either or both docetaxel and vofatamab should be considered: allergic or non-allergic infusion reaction (fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, hypotension, hypersensitivity, anaphylaxis, dyspnea, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress), mucositis, thrombocytopenia, neutropenia, leukopenia, infections, hypersensitivity, diarrhea, anorexia, asthenia/fatigue, flushing, pain and headache. All other AEs not listed in the prior paragraph above may also be attributed to either docetaxel or vofatamab or both.

There are currently no AEs that are more likely attributed to vofatamab and not docetaxel.

Subjects will be closely monitored for platelets and coagulation factors including, aPTT, PT/INR, and fibrinogen (see [Table 1](#) for the timing of assessments). If either aPTT or PT/INR exceeds  $1.5 \times \text{ULN}$ , all study drug treatment should be held until these factors return to baseline levels before redosing. Exceptions may be allowed upon discussion with the Sponsor and Investigator.

##### 5.1.6.2.1 Vofatamab Dose Modification

During Cycle 1, if the Day 8 dose is not completed within the 3-day visit window (i.e., by Day 11) for toxicity issues, the next dose should be withheld until the Day 21 (Cycle 2,



Day 1) administration. Subjects in whom toxicities have not reversed sufficiently by the scheduled day of infusion (for Cycle 2 and beyond) may have their dose of study drug (vofatamab or placebo) delayed by up to 21 days. If all study drug-related (i.e., possibly, probably or definitely related) toxicities have reversed sufficiently and the additional criteria described in [Section 5.1.6.1](#) have been met, then the subject may receive the subsequent dose of study drug (vofatamab or placebo).

Subjects who do not fulfill the criteria for dosing after 21 days have elapsed will be discontinued from study treatment, will undergo End of Treatment/ET visit assessments, and will be followed for safety outcomes for 30 days following the subject's last dose of study drug (vofatamab or placebo) or until the subject receives another anti-cancer therapy, whichever occurs first. Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the subject by the investigator and approval from the Medical Monitor, with the option of dosing study drug (vofatamab or placebo) at the full dose of 25 mg/kg or reducing the dose of study drug (vofatamab or placebo) to 20 mg/kg. In addition, delay of therapy because of toxicities not attributed to study drug (i.e., definitely not related or unlikely related) may not require discontinuation and will be discussed with the Medical Monitor.

#### 5.1.6.2.2 Docetaxel Dose Modification

Subjects who experience either febrile neutropenia, neutrophils  $< 500$  cells/mm<sup>3</sup> for more than one week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment should have study drug (vofatamab or placebo) and docetaxel treatment withheld until resolution of the toxicity. Once the toxicity resolves, subjects should resume treatment with (vofatamab or placebo) and docetaxel according to the site's institutional standard if the AE is deemed by the investigator to be most likely due to docetaxel treatment. An acceptable dose modification regimen is to reduce the dose of docetaxel to 55 mg/m<sup>2</sup>. Subjects who develop Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely (note: subjects who discontinue docetaxel due to lack of tolerability should continue to receive vofatamab as a single-agent until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination).

#### 5.1.7 *Post-Study Access to Study Drug*

The Sponsor does not have any plans to provide vofatamab or other study interventions to subjects after the conclusion of the study or any earlier withdrawal. The Sponsor will evaluate the appropriateness of continuing to provide vofatamab to study subjects after evaluating the primary efficacy outcome measure and safety data gathered in the study.

### 5.2 Preparation, Administration, and Storage of Study Drug

Once a subject is enrolled into Randomized Phase of Phase 2b of the study, the pharmacist will obtain the randomization number and treatment assignment for the subject from the interactive voice/web response system (IVRS/IWRS).



Using the IVRS/IWRS treatment assignment, the pharmacist will then prepare and reconstitute the study drug as appropriate. The pharmacist will also maintain records for drug accountability.

### **5.2.1 Vofatamab**

#### **5.2.1.1 Preparation and Administration**

Vofatamab is provided as a sterile lyophilized powder and contains no preservatives. After reconstitution with sterile water for injection, the drug product is formulated as 10 mg/mL vofatamab in 200 mM arginine succinate, 0.02% polysorbate 20, pH 5.5. Phase 2b sterile liquid formulation of vofatamab in 20-mL single use vials is currently in development with a planned concentration of approximately 50 mg/mL. Details will follow in the IMPD and pharmacy manual at time of introduction of this new formulation.

Compatibility testing has shown that vofatamab as a sterile lyophilized powder is stable when diluted to a concentration at or above 3 mg/mL in 0.45% sodium chloride diluent. Therefore, delivery will be carried out either with or without dilution of the drug product, depending upon the amount of drug administered. When administered undiluted, drug product will be delivered using standard medical syringes, and syringe pump or using IV bags and pump. When diluted, the drug product will be delivered by dilution in 0.45% sodium chloride IV bags with a final vofatamab concentration of 3 mg/mL or higher. In both cases, delivery will be carried out with a 0.22 µm in-line filter, on either the syringe-pump extension set or the IV infusion set.

The initial dose of vofatamab will be administered over 90 (± 15) minutes to well-hydrated subjects. The infusion may be slowed or interrupted for subjects experiencing infusion-associated symptoms. Following the initial dose, subjects will be observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If prior infusions have been well-tolerated, subsequent doses of vofatamab may be administered over 30 (± 10) minutes, followed by a 30-minute observation period post-infusion. Additional instructions on study drug preparation and administration are provided in the Sponsor's Pharmacy Instructions.

#### **5.2.1.2 Storage**

Vofatamab vials must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. Vofatamab should not be used beyond the expiration date provided by the manufacturer. The lyophilized vofatamab vials should be reconstituted with water for injection the day of use. Vial contents should not be frozen or shaken and should be protected from direct sunlight. If not diluted immediately, the reconstituted drug may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Once diluted using half normal saline (0.5 NS; 0.45% sodium chloride), vofatamab solutions may be stored at refrigerated (2–8°C) for 24 hours or at room temperatures (25°C [77°F]) for up to 8 hours prior to use, total time at both temperatures not to exceed 24 hours.

Additional vofatamab dosage, administration, and storage instructions are provided in the [Sponsor's Pharmacy Instructions](#).

### 5.2.1.3 Precautions

Mild infusion reactions have been reported with vofatamab in subjects dosed up to 30 mg/kg vofatamab. Though these reactions were mild, administration of vofatamab will be performed in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. Subjects will be monitored during and after each vofatamab infusion for 90 minutes after the first infusion and for 30 minutes after subsequent infusions in the absence of infusion-related AEs. Subjects who experience infusion-related symptoms should be managed as directed in [Table 4](#) below.

**Table 4 Management of Infusion-Related Symptoms (e.g., fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, hypotension, hypersensitivity, anaphylaxis, dyspnea, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress)**

Infusion-Related Symptoms <sup>a</sup>	Guidance
Grade 1–2	<ul style="list-style-type: none"> <li>• Slow or hold infusion.</li> <li>• Give supportive treatment <sup>b</sup>.</li> <li>• Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion <sup>c</sup>.</li> </ul>
Grade 3–4	<ul style="list-style-type: none"> <li>• Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.</li> </ul>

<sup>a</sup> Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, for the grading of symptoms. This table does not refer to management of IgE-mediated allergic reactions, which should be managed as directed in text following this table.

<sup>b</sup> Supportive treatment: Subjects should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators. For hypotension, subjects may require vasopressors.

<sup>c</sup> Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes.

Subjects who experience vofatamab infusion-related temperature elevations of  $>38.5^{\circ}\text{C}$  or other minor infusion-related symptoms may be treated symptomatically with acetaminophen ( $\geq 500$  mg) and/or H<sub>1</sub> and H<sub>2</sub> histamine-receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen,  $\beta_2$ -agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice. Infusion-related reaction (IRR) prophylaxis with medications (e.g., acetaminophen, antihistamines, and/or corticosteroids) may be instituted at any point in the study that it is determined to be in the best interest of subjects due to the observation of IRRs in a significant number of subjects.

In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events) or immunoglobulin (Ig) E-mediated anaphylactic reaction, vofatamab should

be discontinued and no additional vofatamab should be administered. Subjects who experience these reactions should receive aggressive symptomatic treatment and should be discontinued from study treatment.

Precautions and procedures for suspected anaphylactic reaction during study drug infusions are provided in [Appendix 4](#). Prophylactic administration with acetaminophen and antihistamine may be used at investigator discretion.

### **5.2.2            *Docetaxel***

Premedication with a corticosteroid will be administered according to the site's institutional standard. An acceptable regimen may consist of dexamethasone 8 mg orally, twice-a-day, for 3 days, beginning one day prior to docetaxel infusion. Other pre-medications, such as anti-emetics or antihistamines, may be prescribed, as needed, based on the investigator's assessment.

Complete preparation, administration, and storage instructions for docetaxel are provided in the Sponsor's Pharmacy Instructions.

### **5.2.3            *Placebo***

The placebo will be provided as a sterile liquid formulation in 20-mL single-use vials in identical format to vofatamab

## **5.3                *Study Drug Accounting***

### **5.3.1            *Receipt of Drug Supplies***

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

### **5.3.2            *Return or Destruction of Study Drug***

At the end of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug returned or destroyed on site during the study or at completion of the study, will be documented in the study files.

## **5.4 Method of Assigning Subjects to Treatment Groups**

### **5.4.1 Phase 1b (Cohort 1)**

Subjects will be enrolled into Phase 1b as described in [Section 3.1.1](#)

### **5.4.2 Phase 2 (Cohorts 2 and 3)**

Subjects will be enrolled into Phase 2 as described in [Section 3.1.2](#).

Phase 2b Monotherapy Expansion Subjects will be enrolled into the Phase 2b Monotherapy Expansion as described in [Section 3.1.3.1](#).

### **5.4.3 Phase 2b Randomized Phase**

After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor via facsimile or email of a scanned copy, and obtain the Sponsor's approval to enroll the subject. Once the Sponsor reviews and approves the subject for enrollment, the Sponsor will inform the site and the pharmacist will obtain the subject's randomization number and treatment assignment from the IVRS/IWRS.

Subjects will be assigned in a 2:1 ratio to either Arm A or Arm B by IVRS/IWRS, and the central randomization schedule will have subjects stratified by visceral metastasis (present versus absent).

## **5.5 Blinding of Study Drug**

The subjects and/or legal guardians, Investigators, and all Sponsor personnel and designees involved in the conduct of the study will be blinded to the identity of the study infusions during the Randomized Phase of Phase 2b. The following precautions will be taken to ensure the integrity of the study blind during the Randomized Phase:

- Treatment will not be unblinded for an individual subject, until all subjects have completed the Randomized Phase of the study. By exception, treatment may be unblinded for an individual subject in the event of a medical emergency ([Section 5.5.1](#)).

### **5.5.1 Unblinding**

The unblinding of an individual subject may only occur in the event of a medical emergency, where knowledge of the study drug administered to the subject is essential for medical management of the subject. In the event of a medical emergency requiring unblinding, the Investigator must notify the Medical Monitor immediately.

Emergency unblinding will be managed through IVRS/IWRS. If unblinding should occur, the reason for the unblinding will be recorded in the eCRF.

If a subject's treatment assignment is formally unblinded for any reason, the subject must be discontinued from the double-blind treatment period.

## **5.6 Treatment Compliance**

Subject compliance with treatment is not applicable, since study site personnel will administer study drug.

## **5.7 Concomitant and Prohibited Therapies**

### **5.7.1 Concomitant Therapy**

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject between the screening evaluation and the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Patients receiving an anticoagulant at Screening are excluded. However, treatment with an anticoagulant(s) is permitted for subjects who are on study and receiving vofatamab, if deemed clinically necessary following discussion with the Sponsor and Investigator.

### **5.7.2 Prohibited Therapy**

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy (unless for palliative care of solitary lesions)
- Immunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts)
- Any therapies intended for the treatment of UCC, whether approved by local regulatory authorities or investigational

Subjects who require the use of any of these agents will be discontinued from treatment with study drug. See [Section 6.1.3](#) for assessments that are to be performed for subjects who discontinue from the study early.

## **6 STUDY ASSESSMENTS AND PROCEDURES**

The Schedule of Assessments, Screening through End of Study, is presented in [Table 1](#).

### **6.1 Assessments by Study Visit**

#### **6.1.1 Screening**

The following Screening evaluations will be performed within 28 days preceding Cycle 1, Day 1 of Phase 1b, Phase 2, and Phase 2b (defined as the day of the first dose of study drug), unless otherwise specified.

- Written informed consent must be signed before any study-specific procedures are performed (described in [Section 6.2.1](#))
- A separate informed consent form must be signed for subjects in Phase 2b Monotherapy Expansion participating in the PK Sub-study ([Appendix 8](#)).
- For Cohort 1, archival tumor samples must be available for retrospective sequencing of cancer-related genes, including FGFR3, by NGS.
- For Cohorts 2 and 3 of Phase 2 and all subjects in Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase, subjects must be confirmed to have a FGFR3 genomic alteration at the time of documentation of advanced disease. Available tissue that was obtained at or after the time the subject was found to have muscle invasive disease and is of suitable quality and quantity (as outlined in the Sponsor's Laboratory Instructions) should be used to assess the FGFR3 status by genetic testing. A blood sample to assess the FGFR3 status of circulating tumor DNA by genetic sequencing must also be provided. (described in [Section 6.2.2](#)). In case no archival tissue sample is available or tissue testing was not informative, a blood sample to assess the FGFR3 status by circulating tumor DNA (ctDNA) can be submitted and if positive will be considered adequate for inclusion. For subjects participating in Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase, if suitable archival tissue is unavailable and ctDNA is not informative, then a core biopsy of tumor tissue (metastatic or primary from any anatomical location except the bone, lung or brain) can be obtained to determine FGFR3 status.
- Review inclusion/exclusion criteria (described in [Section 6.2.3](#))
- Medical history and demographics (described in [Section 6.2.4](#))
- Complete physical examination (described in [Section 6.2.5](#))
- Height and weight
- Vital signs (described in [Section 6.2.6](#))
- ECOG PS
- Concomitant medications

- Tumor assessment: A documented standard-of-care tumor assessment performed within 28 days prior to Cycle 1, Day 1 may be used for the screening assessment (described in [Section 6.2.8](#) and [Appendix 3](#))
- CT or MRI of the brain
- Hematology (described in [Section 6.2.9.2](#))
- Serum chemistry (described in [Section 6.2.9.2](#))
- ECG (described in [Section 6.2.10](#))
- Coagulation (i.e., aPTT, PT/INR, fibrinogen)
- Urine or serum pregnancy test (described in [Section 6.2.9.2](#))
- HBV and HCV screening (described in [Section 6.2.9.2](#))
- Urinalysis (described in [Section 6.2.9.2](#))
- In Cohort 1 (Phase 1b) and Cohorts 2 and 3 (Phase 2): PROMIS Global Physical Health (GPH) Short Survey (described in [Section 6.2.11](#) and [Appendix 5](#))
- In Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase: European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30; described in [Section 6.2.12](#) and [Appendix 7](#))

#### **6.1.2 Phase 1b, Phase 2 and Phase 2b (Cycle 1 Through Cycle 12 and Beyond: Week 1 Through Week 36 and Beyond)**

All screening evaluations must be completed and reviewed by the Medical Monitor to confirm that subjects meet all eligibility criteria and are approved for enrollment before the first infusion of study drug. Procedures and assessments are summarized in the Schedule of Assessments ([Table 1](#)). Study treatment with vofatamab and docetaxel or vofatamab alone may continue until disease progression, unacceptable toxicity, death, or study exit, including withdrawal of patient consent or study termination.

All visits should occur on the scheduled days. However, visits may occur  $\pm 3$  days from the scheduled date, if a change is required for logistical/scheduling reasons. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug infusion, unless otherwise noted.

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle, unless otherwise specified. Results must be reviewed and the review documented prior to study drug administration.

Up to 10 subjects at designated centers in Phase 2b Monotherapy Expansion ([Appendix 8](#)) who provide separate informed consent will participate in a PK Sub-study and will have



intensive PK sample collection (samples obtained before and 30 minutes post-dosing) performed on Day 1 of Cycles 1, 2, 3, 5, 6, 10 and end of treatment following the initiation of vofatamab dosing. In addition, for Cycle 1, samples will be collected on Day 2 and 4, and on Day 8 before and 30 minutes post-dosing. In Cycle 5, samples will be collected on Day 2, Day 8, Day 15, and Day 21.

#### 6.1.2.1 Cycle 1, Day 1

The following assessments should be performed prior to study drug infusion:

- Targeted physical examination (described in [Section 6.2.5](#))
- Weight
- Vital signs (described in [Section 6.2.6](#))
- ECOG PS
- Concomitant medications
- Hematology (described in [Section 6.2.9.2](#))
- Serum chemistry (described in [Section 6.2.9.2](#))
- ECGs (described in [Section 6.2.10](#))
- If the subject enrolled in the study based on genetic testing of solid tumor (archival or biopsy), a blood sample for genetic testing of circulating tumor DNA will be obtained to verify the results
- Coagulation (i.e., aPTT, PT/INR, fibrinogen)
- Urine or serum pregnancy test (described in [Section 6.2.9.2](#))
- Urinalysis (described in [Section 6.2.9.2](#))
- Urine biomarker sample collection (described in [Section 6.2.9.1](#))
- ATA samples will be drawn predose on Day 1 of Cycle 1 (described in [Section 6.2.9.1](#))

Study drug administration:

- Subjects should be well-hydrated prior to study drug administration.
  - Subjects in Cohorts 1 (Phase 1b), 2 (Phase 2), and Phase 2b Randomized Phase: Subjects will receive one IV infusion of docetaxel, over approximately 60 minutes, followed by one IV infusion of study drug (vofatamab for Cohorts 1 and 2 and blinded vofatamab [Arm A] or placebo [Arm B] in Phase 2b Randomized Phase. The study drug (vofatamab or placebo) IV infusion will begin approximately 30 minutes after completion of the docetaxel infusion and will be conducted over 90 ( $\pm$  15)



minutes. Infusions will be followed by a 90-minute observation period (described in [Section 5.2](#))

- Subjects in Cohort 3 (Phase 2) and Phase 2b Monotherapy Expansion: Subjects will receive one IV infusion of vofatamab over 90 ( $\pm$  15) minutes. Infusions will be followed by a 90-minute observation period (described in [Section 5.2](#))
- PK samples for the assessment of vofatamab will be collected within 30 ( $\pm$  15) minutes after completion of docetaxel infusion and before study drug (vofatamab or placebo) infusion (described in [Section 6.2.9.1](#)).
- Vital signs should be assessed every 15 ( $\pm$  5) minutes during the study drug infusion, and at the end of the infusion (described in [Section 6.2.6](#))
- AEs should be collected and recorded while the subject is receiving study drug

The following assessment(s) should be performed after study drug infusion has been completed:

- ECGs should be collected 30 ( $\pm$  15) minutes and 2-hours ( $\pm$  15 minutes) post infusion with study drug (described in [Section 6.2.10](#))
- Vital signs should be assessed every 30 ( $\pm$  10) minutes for 90 minutes post-infusion (described in [Section 6.2.6](#))
- PK samples for vofatamab will be collected within 30 ( $\pm$  15) minutes after completion of study drug (vofatamab or placebo) infusion (described in [Section 6.2.9.1](#))
- AEs: Subjects should be monitored for 90 minutes following completion of the infusion
- Survival

#### 6.1.2.2 Cycle 1, Day 8

The following assessments should be performed prior to study drug infusion:

- Weight
- Vital signs (described in [Section 6.2.6](#))
- Hematology (described in [Section 6.2.9.2](#))
- Coagulation (i.e., aPTT, PT/INR, fibrinogen)
- AEs since the previous visit
- Concomitant medications

Study drug administration:

- Subjects should be well-hydrated prior to study drug administration. Subjects in Cohorts 1 to 3, Phase 2b Monotherapy Expansion, and Phase 2b Randomized Phase Arm A will receive one IV infusion of vofatamab, 25 mg/kg, over 90 ( $\pm$  15) minutes. Subjects in Phase 2b Randomized Phase Arm B will receive one IV infusion of placebo over 90 ( $\pm$  15) minutes. (Note: If the prior study drug (vofatamab or placebo) infusion was well-tolerated, the infusion on Day 8 may be administered over 30 [ $\pm$  10] minutes). Infusions will be followed by a 30-minute observation period (described in [Section 5.2](#)).
- PK samples for the assessment of vofatamab will be collected before study drug (vofatamab or placebo) infusion (described in [Section 6.2.9.1](#)).
- Vital signs should be assessed every 15 ( $\pm$  5) minutes during the infusion, and at the end of the infusion (described in [Section 6.2.6](#)).
- AEs should be collected and recorded while the subject is receiving study drug

The following assessment(s) should be performed after study drug infusion has been completed:

- Vital signs should be assessed every 30 ( $\pm$  10) minutes (described in [Section 6.2.6](#))
- PK samples will be collected within 30 ( $\pm$  15) minutes after completion of study drug (vofatamab or placebo) infusion (described in [Section 6.2.9.1](#))
- AEs: Subjects should be monitored for 30 minutes following completion of the infusion
- Survival

6.1.2.3 Cycle 1, Day 15 (Phase 1 and 2 only)

- CBC (described in [Section 6.2.9.2](#))

6.1.2.4 Cycles 2-12 and Beyond, Day1

Prior tumor assessment results must be reviewed before study drug infusion. Continuation in the study will be based on the tumor assessment results.

The following assessments should be performed prior to study drug infusion:

- Targeted physical examination (described in [Section 6.2.5](#))
- Weight
- Vital signs (described in [Section 6.2.6](#))
- ECOG PS
- AEs since the previous visit

- Concomitant medications
- Tumor assessments should be performed every 9 weeks  $\pm$  1 week and prior to start of next infusion (i.e., every third cycle beginning at the Screening visit; described in [Section 6.2.8](#))
- Hematology (described in [Section 6.2.9.2](#))
- Serum chemistry (described in [Section 6.2.9.2](#))
- Coagulation (i.e., aPTT, PT/INR, fibrinogen)
- Urine or serum pregnancy test (described in [Section 6.2.9.2](#))
- Urinalysis (described in [Section 6.2.9.2](#))
- ECG (described in [Section 6.2.10](#))
- ATA samples will be drawn predose on Day 1 of Cycle 5 only
- In Cohort 1 (Phase 1b) and Cohorts 2 and 3 (Phase 2): PROMIS GPH Short Survey should be performed at the end of every third cycle (i.e., end of Cycles 3, 6, 9, and 12; or Week 9 and every 9 weeks thereafter for up to 36 weeks; described in [Section 6.2.11](#))
- In Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase: the EORTC QLQ-C30 instrument should be performed at the end of every third cycle (i.e., end of Cycles 3, 6, 9, and 12; or Week 9 and every 9 weeks thereafter for up to 36 weeks, described in [Section 6.2.12](#)).

Study drug administration:

- Subjects should be well-hydrated prior to study drug administration.
  - Subjects in Cohort 1 of Phase 1b, Cohort 2 of Phase 2, and all subjects in Phase 2b Randomized Phase: Subjects will receive one IV infusion of docetaxel, over approximately 60 minutes, followed by one IV infusion of study drug (vofatamab in Cohorts 1 and 2 and blinded vofatamab [Arm A] or placebo [Arm B] in Randomized Phase) The study drug (vofatamab or placebo) infusion will begin approximately 30 minutes after completion of the docetaxel infusion and will be conducted over 90 ( $\pm$  15) minutes. (Note: If prior study drug (vofatamab or placebo) infusions have been well-tolerated, doses of study drug (vofatamab or placebo) during Cycles 2-12 and beyond may be administered over 30 [ $\pm$  10 minutes]). Infusions will be followed by a 30-minute observation period (described in [Section 5.2](#))
  - Subjects in Cohort 3 of Phase 2 and in Phase 2b Monotherapy Expansion of Phase 2b: Subjects will receive one IV infusion of vofatamab. (Note: If prior vofatamab infusions have been well-tolerated, doses of vofatamab during Cycles 2-12 and beyond may be administered over 30 [ $\pm$  10 minutes]). Infusions will be followed by a 30-minute observation period (described in [Section 5.2](#))

- PK samples for the assessment of vofatamab will be collected within 30 ( $\pm 15$ ) minutes after completion of docetaxel infusion and before study drug (vofatamab or placebo) infusion on Day 1 of Cycles 2, 5, and 10.
- Vital signs should be assessed every 15 ( $\pm 5$ ) minutes during the infusion, and at the end of the infusion (described in [Section 6.2.6](#))
- ECGs should be collected on Day 1 of Cycles 2 and 5 (described in [Section 6.2.10](#))
- AEs should be collected and recorded while the subject is receiving study drug

The following assessment(s) should be performed after study drug infusion has been completed:

- Vital signs should be assessed every 30 ( $\pm 10$ ) minutes post-infusion (described in [Section 6.2.6](#))
- Urine biomarker sample collection within 60 minutes post-infusion on Day 1 of Cycles 2 and 5 (described in [Section 6.2.9.1](#))
- PK samples will be collected within 30 ( $\pm 15$ ) minutes after completion of study drug (vofatamab or placebo) infusion on Day 1 of Cycles 2, 5 and 10.
- AEs: Subjects should be monitored for 30 ( $\pm 10$ ) minutes following completion of the infusion
- Survival

### **6.1.3            *End of Treatment/Early Termination***

Subjects who complete the study or discontinue from the study early will be asked to return to the clinic within 30 days after the last study drug infusion for an End of Treatment/ET visit. The visit at which response assessment shows progressive disease may be used as the End of Treatment/ET visit.

The following assessments should be performed:

- Targeted physical examination (described in [Section 6.2.5](#))
- Weight
- Vital signs (described in [Section 6.2.6](#))
- ECOG PS
- Adverse events
- Concomitant medications

- Tumor assessment; subjects will also be asked to provide an optional metastatic tumor tissue sample (biopsy) at End of Treatment or at autopsy (described in [Section 6.2.8](#)).
- Hematology (described in [Section 6.2.9.2](#))
- Serum chemistry (described in [Section 6.2.9.2](#))
- ECG (described in [Section 6.2.10](#))
- Coagulation (i.e., aPTT, PT/INR, fibrinogen)
- Urine or serum pregnancy test (described in [Section 6.2.9.2](#))
- Urine biomarker sample collection (described in [Section 6.2.9.1](#))
- PK (described in [Section 6.2.9.1](#))
- ATA (described in [Section 6.2.9.1](#))
- Blood for circulating tumor DNA (ctDNA) will be collected at the time of progression.
- In Cohort 1 (Phase 1b) and Cohorts 2 and 3 (Phase 2): PROMIS GPH Short Survey (described in [Section 6.2.11](#))
- In Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase: EORTC QLQ-C30 (described in [Section 6.2.12](#))
- Survival

#### **6.1.4            *End of Study***

All subjects will be monitored for survival every 3 months via telephone follow-up from the investigator until death or full withdrawal of consent.

### **6.2                Description of Assessments and Procedures**

#### **6.2.1            *Informed Consent***

The potential subject or legal guardian of a potential subject will be given a verbal explanation of the study and the procedures involved and will have all questions addressed. The subject or legal guardian must sign and date a consent form that has been approved by the appropriate Institutional Review Board/Ethic Committee (IRB/EC) before any study-specific procedures are initiated. The subject's or legal guardian will be given a copy of the signed and dated informed consent form.

Informed Consent Forms for subjects who are not subsequently enrolled will be maintained at the study site.

### **6.2.2            *Archival Tissue Collection***

For Phase 1b (cohort 1), all subjects in this study must consent to submit archival tumor tissue. Availability of archival tumor tissue should be confirmed prior to study entry, requested from the appropriate institution after study entry, and sent to the appropriate laboratory as soon after the administration of the first dose as possible. Archival tissue specimens will be analyzed for FGFR3 expression, mutations and FGFR3-TACC3 fusions. Testing will be completed after study entry.

For Cohorts 2 and 3 of Phase 2 and all subjects in Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase, subjects must be confirmed to have a FGFR3 genomic alteration at the time of documentation of advanced disease. Available tissue that was obtained at or after the time the subject was found to have muscle invasive disease and is of suitable quality and quantity (as outlined in the Sponsor's Laboratory Instructions) should be used to assess the FGFR3 status by genetic testing. A blood sample to assess the FGFR3 status of circulating tumor DNA by genetic sequencing must also be provided. (described in Section 6.2.2). In case no archival tissue sample is available or tissue testing was not informative, a blood sample to assess the FGFR3 status by circulating tumor DNA (ctDNA) can be submitted and if positive will be considered adequate for inclusion. For subjects participating in Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase, if suitable archival tissue is unavailable and ctDNA is not informative, then a core biopsy of tumor tissue (metastatic or primary from any anatomical location except the bone, lung or brain) can be obtained to determine FGFR3 status. Other exploratory studies (e.g., determining whether genetic alterations in FGFR3 or other cancer-related genes that may act cooperatively with FGFR3 in promoting tumor growth and invasion are present) may also be conducted on these samples by the Sponsor or a central laboratory.

After analysis, any remaining tissue blocks from archival biopsies will be returned to the facility from which they were obtained.

Detailed instructions will be provided in the Sponsor's Laboratory Instructions.

### **6.2.3            *Subject Eligibility***

During the Screening visit, all subjects will be assessed for eligibility against the inclusion and exclusion criteria described in [Section 4.1](#) and [Section 4.2](#).

### **6.2.4            *Medical History and Demographics***

Complete medical history will be recorded at the Screening visit.

### **6.2.5            *Physical Examination, Height, and Weight***

Complete physical examinations should include the evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, those systems associated with symptoms, and any system that might be associated with tumor assessment).

Changes from baseline for all targeted physical examinations should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

Height should be measured only at the Screening visit and weight should be measured at the Screening visit and on Day 1 of each cycle.

#### **6.2.6           Vital Signs**

Vital signs will be measured while the subject is in a supine or sitting position and will include measurements of systolic and diastolic blood pressure, pulse rate, and body temperature. Ensure the same method for each subject during the study period.

On Cycle 1 Day 1 and Cycle Day 8, vital signs for vofatamab should be assessed pre-infusion, every 15 ( $\pm$  5) minutes during the infusion, at the end of the infusion, and 30 ( $\pm$  10) minutes, 60 ( $\pm$  10) minutes, and 90 ( $\pm$  10) minutes post-infusion. On subsequent cycles, vital signs for vofatamab should be assessed pre-infusion as clinically indicated, and post infusion. For infusions with docetaxel, vital signs should be assessed per institutional guidelines, or regional label. Vital signs also will be measured at the End of Treatment/ET visit.

#### **6.2.7           Adverse Events**

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Subjects will be monitored for any untoward effects during study drug infusion and for 90 minutes following completion of the first infusion on Day 1 of Cycle 1, and for 30 minutes in the absence of infusion-related AEs at subsequent infusions. All AEs will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Follow-up for AEs will occur for 30 days after the subject's last dose of study drug or until initiation of another anti-tumor therapy, whichever occurs first.

Safety assessment guidelines are described in [Section 8](#).

#### **6.2.8           Tumor and Response Assessments**

For subjects with measurable disease, response will be reported by the investigator per RECIST v1.1 (see [Appendix 3](#)) and reviewed by the Medical Monitor.

- All evaluable and measurable disease must be documented at the Screening visit and re-assessed every 9 weeks  $\pm$  1 week until disease progression or lack of tolerability; and

will include the following measures CT scans of the chest, abdomen, and pelvis, and all known or suspected sites of disease

- Brain scan (CT or magnetic resonance imaging [MRI]) (Screening only)
- Bone scans (CT or MRI), if clinically indicated

Additional methods of assessment of measurable disease per RECIST v1.1 may be used in addition to those listed above. The same imaging methods used at screening must be used throughout the study for each subject. Additional tumor assessments may be conducted as clinically indicated during the study. Results must be reviewed prior to study drug infusion at the next cycle to assess whether a subject is eligible to continue treatment. A tumor assessment scan should be performed if the subject is discontinuing the study early.

At the End of Treatment/ET visit, subjects will be asked to provide any optional metastatic tumor tissue samples collected during the study or at autopsy.

### **6.2.9            *Laboratory Assessments***

Local laboratory assessments may be performed within 72 hours preceding study drug administration on Day 1 of each cycle, unless otherwise specified. Results must be reviewed and the review documented prior to study drug administration.

Instruction manuals and supply kits will be provided for all central laboratory assessments.

Detailed sample collection instructions will be provided in the Sponsor's Laboratory Instructions.

#### **6.2.9.1            Central Laboratory Assessments**

At select sites, samples for biomarkers, anti-vofatamab and PK assays will be collected and will be sent to one or more laboratories for analyses.

- Urine or blood biomarker assessments: Biomarkers will be assessed for all subjects. Urine samples will be obtained from all subjects before the administration of study drug (vofatamab or placebo) on Day 1 of Cycle 1, after the administration of study drug (vofatamab or placebo) on Day 1 of Cycles 2, and 5. Blood for circulating tumor DNA (ctDNA) will be collected at the time of progression. Urine will also be collected for assessment of biomarkers at EOT. (Table 1).

Biomarker urine and blood sample collection instructions are described in the Sponsor's Laboratory Instructions.

- ATA assessments: As expected with any recombinant antibody, vofatamab may elicit an immune response and subjects may develop antibodies against vofatamab. Although ATAs directed against vofatamab are not expected to result in significant clinical consequence, subjects will be monitored for any potential immune response to vofatamab in this clinical study. Blood samples from all subjects treated will be obtained prior to



study drug (vofatamab or placebo) infusion on Day 1 of Cycles 1, 5 and at the End of Treatment/ET Visit.

Serum samples will be analyzed using a validated assay for the determination of antibodies to vofatamab in human serum. Additional details are provided in the Sponsor's Laboratory Instructions.

- **PK assessments:** PK will be assessed for vofatamab for all subjects. Blood samples will be obtained from all subjects 30 ( $\pm$  15) minutes before study drug (vofatamab or placebo) infusion, and within 30 ( $\pm$  15) minutes after the end of study drug (vofatamab or placebo) infusion on Days 1 and 8 of Cycle 1, Day 1 of Cycles 2, 5, and 10 and once at the End of Treatment/ET visit ([Table 1](#)).

Subjects in Phase 2b Monotherapy Expansion of Phase 2b that consented to the optional PK Sub-study will have intensive PK sample collection ([Appendix 8](#)).

Serum samples will be analyzed for the quantitative determination of vofatamab in human serum. Additional details are provided in the Sponsor's Laboratory Instructions.

#### 6.2.9.2 Local Laboratory Assessments

Samples for hematology, serum chemistry, pregnancy, and urinalysis will be analyzed at the study site's local laboratory.

- Hematology: complete blood count (complete blood count [CBC]; including hemoglobin, hematocrit, red blood cell [RBC], WBC), platelet count, and percent and absolute differential count (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells)
- Coagulation: activated partial thromboplastin time (aPTT), PT/INR, fibrinogen
- Serum chemistry: sodium, potassium, chloride, bicarbonate, non-fasting glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphate, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, lactate dehydrogenase, and uric acid
- Viral serology and detection: Hepatitis B (HBsAg and HBcAb; also HBV DNA by PCR if the subject is HBcAb positive), HCV antibody at Screening
- Urine or serum pregnancy test: For women of childbearing potential, a urine or serum pregnancy test must be performed at Screening, prior to administration of study drug on Day 1 of each cycle, and at the End of Treatment/ET visit.
- Urinalysis:
  - Macroscopic examination: specific gravity, pH, protein, glucose, ketones, blood, bilirubin, leukocyte esterase, urobilinogen, and nitrite
  - Microscopic examination: RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast

#### **6.2.10            *Electrocardiogram Assessments***

ECG measurements must be obtained from subjects who have been resting in a supine or sitting position for at least 10 minutes, either before or after drawing blood samples. One ECG reading should be obtained at each of the following time points: Screening; Cycle 5, Day 1 (prior to infusion with study drug); and at the End of Treatment Visit. ECGs (at least 3 readings) should be obtained at the following time points: Cycle 1, Day 1 (prior to infusion with study drug; 30 ( $\pm$  15) minutes and 2 hours ( $\pm$  15 minutes) post infusion with study drug); and Cycle 2, Day 1 (prior to infusion with study drug) (described in [Section 6.1](#) and [Table 1](#)).

#### **6.2.11            *PROMIS Global Physical Health Short Survey***

In Cohort 1 (Phase 1b) and Cohorts 2 and 3 (Phase 2), the PROMIS GPH Short Survey is a self-administered, 4 question, survey which assesses overall physical health, physical function, pain, and fatigue ([Hays 2009](#)). The GPH Short Survey will be administered at the Screening visit, at the end of every third cycle (i.e., end of Cycles 3, 6, 9, and 12; or Week 9 and every 9 weeks thereafter for up to 36 weeks, before pre-medication and administration of the next dose) and at the End of Treatment/ET visit. The survey is provided in [Appendix 5](#).

#### **6.2.12            *European Organization for Research and Treatment Quality of Life Questionnaire***

In Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase, the EORTC QLQ-C30 assesses the quality of life (disease and treatment-related symptoms, physical, psychological, and social functioning) of cancer patients using a self-reported questionnaire. The EORTC QLQ-C30 will be assessed at the Screening visit, at the end of every third cycle (i.e., end of Cycles 3, 6, 9, and 12; or Week 9 and every 9 weeks thereafter for up to 36 weeks, before pre-medication and administration of the next dose) and at the End of Treatment/ET visit. The survey is provided in [Appendix 7](#).

#### **6.2.13            *Survival***

Upon discontinuation of study treatment, subjects will be followed for overall survival every 3 months via telephone until death or full withdrawal of consent.

The End of Study visit assessment should be performed by telephone call.

### **6.3                *Appropriateness of Measurements***

The efficacy and safety assessments for this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

## **7 STATISTICAL PLAN**

This section will outline the planned analysis for this study. Analysis will be done for the Phase 1b, Phase 2, Phase 2b Monotherapy Expansion, and Phase 2b Randomized Phase separately.

In general, continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category.

Complete details of the prospective analyses and procedures for handling missing/spurious data handling will be provided in the Statistical Analysis Plan.

The final analysis will occur once 160 subjects have enrolled in Phase 2b Randomized Phase and followed for 12 months. All summaries will be presented by assigned treatment arm.

### **7.1 Sample Size Determination for All Phases**

Phase 2 has two cohorts of 20 subjects each (Cohorts 2 and 3). At the end of Cohort 3 of Phase 2 (N = 20), there is approximately 88% power to detect a difference between a median PFS of 5.5 months in vofatamab monotherapy arm versus 2.5 months from historical data using one sample log-rank test at one-sided alpha level of 0.025 ([Finkelstein, 2003](#); [Woolson, 1981](#); [Lachin, 1986](#)).

The planned sample size for Phase 2b Monotherapy Expansion (up to 80 subjects) is mainly based on the safety requirement, with the power to detect a difference between a median OS of 12.0 months in vofatamab monotherapy arm versus 7.0 months from historical data being approximately 97% using a one sample log-rank test at one-sided alpha level of 0.025.

The primary efficacy endpoint of the Phase 2b Randomized Phase is designed to compare PFS in subjects with UCC who are treated with vofatamab plus docetaxel versus placebo plus docetaxel. The planned sample size of approximately 160 subjects (107 treated with vofatamab plus docetaxel and 53 treated with placebo plus docetaxel) will provide 99% power to detect a difference between a median PFS of 5.5 months in vofatamab plus docetaxel arm versus 2.5 months in the placebo plus docetaxel arm (hazard ratio = 0.46) at alpha = 0.025 (one-sided). This also assumes a 24-month accrual period, 12-month follow-up, 10% of dropout rate within 2 years, and an exponential distribution of PFS event times. In addition, this sample size has approximately 97% power to detect a difference between a median OS of 15 months in vofatamab plus docetaxel arm versus 7.0 months in the placebo plus docetaxel arm (hazard ratio = 0.47).

### **7.2 Phase 1b and Phase 2**

Descriptive statistics will be utilized to present the MTD, safety, and efficacy results for Cohort 1 (Phase 1b) and Cohorts 2 and 3 (Phase 2), as appropriate. The remaining subsections will focus on Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase.

### **7.3 Phase 2b Monotherapy Expansion**

Disposition, demographic, and baseline characteristics will be summarized with descriptive statistics, including sample size, mean, median, standard deviation, and range for continuous variables and frequency counts and percentages for categorical data.

The primary efficacy outcome measure will be PFS, defined as the time from randomization to first occurrence of disease progression (per RECIST v1.1) or death, whichever occurs first. If a subject does not experience progressive disease (PD) or death, PFS will be censored at the day of the last adequate tumor assessment. PFS will be reported by the Investigator at each site and reviewed by the Medical Monitor.

The analysis of the primary efficacy endpoint of PFS will be based on subjects who received at least 1 dose of vofatamab. The Kaplan-Meier (KM) curves will be presented with calculation of median time (months) and its 95% confidence limits. One sample log-rank test for the median PFS in the vofatamab versus historical median PFS of 2.5 months will be performed.

The analysis method for PFS will be repeated for overall survival (OS), the key secondary endpoint. One sample log-rank test for the median OS in the vofatamab versus historical median OS of 7 months will be performed.

In addition, best overall response will be summarized. The number and percentage of subjects who had confirmed complete response (CR) or partial response (PR) as assessed by the investigator using RECIST 1.1 criteria will be provided for subjects who received at least 1 dose of vofatamab.

Safety data including ATAs, AEs, changes in key laboratory test results, ECGs, and changes in vital signs will be summarized for subjects who received at least 1 dose of vofatamab.

#### **7.3.1 Pharmacokinetic Sub-Study**

For PK, plasma concentrations of vofatamab over time will be summarized using descriptive statistics. PK parameters (e.g.,  $C_{max}$ ,  $AUC_{t1/2}$ ) may be listed and summarized using descriptive statistics. Details of an integrated population PK analysis will be provided in the PK reporting and analysis plan.

### **7.4 Phase 2b Randomized Phase**

#### **7.5 Efficacy Analysis**

##### **7.5.1 Primary Efficacy Endpoint**

The primary efficacy outcome measure will be PFS, defined as the time from randomization to first occurrence of disease progression (per RECIST v1.1) or death, whichever occurs first. If a subject does not experience PD or death, PFS will be censored at the day of the last adequate tumor assessment. PFS will be reported by the investigator and reviewed by the Medical Monitor.

The analysis of the primary efficacy endpoint of PFS will be based on the ITT population. PFS will be summarized with hazard ratios, Kaplan-Meier (KM) curves, KM proportions at select time points, KM quartiles (when estimable), the number of subjects with events, the number of subjects censored, and the pattern of censoring. Point estimates for efficacy endpoints will be accompanied by 2-sided 95% confidence intervals including estimates of KM quartiles (Brookmeyer and Crowley, 1982), KM proportions (Kalbfleisch and Prentice, 1980), and binomial proportions (Clopper and Pearson, 1934).

The hypothesis test of the primary efficacy endpoint will be performed using an overall one-sided significance level of 0.025. The stratified log-rank test with a covariate to control for the stratification factor of visceral metastasis (present versus absent) will be performed on the ITT population to test the superiority of Arm A over Arm B.

A sensitivity analysis will also be performed on the EE analysis set (if applicable).

### **7.5.2 Secondary Efficacy Endpoints**

To maintain an upper boundary on the overall experiment-wise type I error rate, hypothesis testing of the secondary efficacy endpoints on the ITT population will follow a closed testing procedure. Inferential comparisons between treatment groups for one or more of the following efficacy endpoints, listed in rank order of importance, will be made provided the null hypothesis associated with the final analysis of PFS is rejected at the statistical significance level of one-sided 0.025.

Rank order of efficacy endpoints for analyses:

1. PFS (Primary Endpoint)
2. OS (Key Secondary Endpoint)
3. ORR

Inferential testing of the secondary efficacy endpoints will proceed in a sequential step-down manner, provided the null hypothesis associated with the previously tested endpoint is rejected at the pre-defined statistical significance level. Otherwise, no further inferential testing will be conducted.

If formal inferential statistical testing is stopped due to the closed testing procedure, inferential statistics may be employed for the remaining secondary efficacy endpoints.

Definitions of Secondary Endpoints:

- ORR is defined as the percentage of subjects who have baseline measurable disease and who achieve a best response of either complete response (CR) or partial response (PR) as assessed by the investigator using RECIST 1.1 criteria. Subjects who do not achieve a CR or PR will be counted as a non-responder. Estimate and exact 95% CI will be provided for ORR by treatment arms.

- OS defined as the time from randomization to death from any cause. For subjects who are alive at the time of analysis data cutoff, OS time will be censored at the last date the subject was known to be alive. Survival time for subjects with no post-baseline survival information will be censored on the date of randomization.
- Medical time to response (TTR) defined as the time to the first occurrence of a documented response.
- DOR, defined as the first occurrence of a documented, objective response until the time of relapse or death from any cause. This will be calculated only for subjects who had a confirmed overall response of CR or PR. In the absence of confirmation of death or progressive disease, duration of response will be censored at the last adequate disease assessment date.
- DCR defined as the percentage of subjects who achieve either CR or PR or SD, as assessed by the investigator per RECIST v1.1.
- DCR (90), defined as the absence of disease progression and death 90 days from the time of randomization as assessed by the investigator using RECIST v1.1.
- DCR (150), defined as the absence of disease progression and death 150 days from the time of randomization as assessed by the investigator using RECIST v1.1.
- QOL, as assessed by EORTC QLQ-C30 (in Phase 2b Monotherapy Expansion and Phase 2b Randomized Phase) will be scored per standard methodology developed for the survey. Results will be compared between treatment groups; changes from baseline will also be calculated. Ad hoc analyses of individual questions relevant to side effects from each treatment may also be performed.

The time-to-event (OS, TTR, DOR) variables will be summarized by the method described for PFS except that DOR will be based on responders.

For categorical response variables (i.e., ORR, DCR), the frequency count, percentage, and exact 95% confidence intervals will be summarized for subjects randomized to the two treatments. The response rates will be compared between the randomized groups via the stratified Cochran-Mantel-Haenszel test based on the ITT population.

## **7.6 Exploratory Endpoints**

The association between FGFR3 mutations or fusions and other biomarkers and efficacy and AE outcomes will be explored.

Plasma concentrations of vofatamab over time will be summarized using descriptive statistics. PK parameters (e.g., C<sub>max</sub>, AUC, t<sub>1/2</sub>) may be listed and summarized using descriptive statistics.

## **7.7 Safety**

Safety will be assessed through summaries of AEs, changes in key laboratory test results, ECGs, and changes in vital signs. The number and percentage of subjects with confirmed positive ATA will be summarized descriptively by scheduled time point. All subjects who receive any amount of vofatamab or docetaxel will be included in the safety analysis.

The safety data will be presented by treatment study arm in individual subject listings and summary tables.

### **7.7.1 Adverse Events**

Overall incidences of all AEs occurring on or after treatment on Day 1 will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and NCI CTCAE v4.0 toxicity grade for both study treatment groups. Each subject will be counted only once within a system organ class or a preferred term by using the AEs with the highest severity (per CTCAE v4.0) within each category. AEs will also be summarized by system organ class, preferred term, toxicity grade (including  $\geq$  Grade 3), and relationship to treatment. AE onset will be shown relative (in number of days) to the day of the first study treatment.

All information pertaining to AEs noted during the study will be listed per subject, detailing verbatim, MedDRA preferred term, MedDRA system organ class, start date, stop date, toxicity grade, and relationship to study treatment. Additionally, all dose modifications and treatment delays and associated AEs will be summarized in a listing.

Subjects who discontinued treatment due to AEs, experienced SAEs, including deaths, will be listed separately and summarized by treatment group.

## **7.8 Analysis Populations**

Safety Population: The safety population will consist of all subjects that receive at least one dose of study drug. All subjects receiving a dose of study drug will be included in all safety summaries.

Intent-To-Treat Population (ITT): The primary efficacy analysis will be performed on the ITT population defined as all subjects who were randomized to study treatment.

Efficacy Evaluable (EE): The EE population will include all subjects randomized and who received study treatment but excluding those identified as major protocol violators and those who discontinued the study within one week of first study drug administration. In addition, subjects in the EE population will be analyzed according to the study medication which they have taken, even if they were not randomized to that arm. If fewer than 5% subjects are excluded from the EE population, no analysis will be performed by EE population.

## **7.9 Subject Disposition**

The disposition of subjects will be tabulated for all subjects. The number of subjects allocated into the study will be summarized by treatment group. Subjects who discontinue treatment, are removed from the study, randomization errors, major protocol violations, will also be tabulated by treatment group.

## **7.10 Demographic and Baseline Characteristics**

Demographic and baseline characteristics will be summarized with descriptive statistics, including sample size, mean, median, standard deviation, and range for continuous variables and frequency counts and percentages for categorical data. The demographic and baseline characteristics will be compared between the two arms to assess the degree to which randomization achieved comparability between treatment arms. A one-way analysis of variance (ANOVA) with factors of treatment will be used for continuous variables. A Fisher's exact test will be used for categorical variables.

## **7.11 Medical History and Physical Examination**

The medical history and physical examination of each subject will be presented in subject listings. No statistical tests will be performed.

## **7.12 Study Drug Administration**

The total number of doses administered, the median (range) number of doses administered, dose modifications, dose delays, dose omissions, and reasons for deviation from planned therapy will be described by study treatment arm.

## **7.13 Laboratory Tests**

Descriptive summary statistics (mean, standard deviation, median, minimum, maximum, frequencies, and percentages, as appropriate) for key laboratory values will be presented at baseline and the follow-up time points for each study treatment group.

In addition, changes in key laboratory data will be summarized by grade using NCI CTCAE v4.0. Shift tables will be used for key laboratory parameters showing the number of subjects who experience changes in laboratory grade during the course of the study compared to baseline will be displayed for each study treatment group.

Grade 3 and 4 laboratory values and laboratory values outside the normal range will be flagged in the data listings.

## **7.14 Vital Signs and Physical Examination**

Vital signs (including temperature, respiratory rate, blood pressure, heart rate, and weight) will be presented descriptively at baseline and for each follow-up time point for each study treatment group. The number (n), mean, standard deviation, median, range will be presented. Changes from baseline to each time point will also be summarized.



Clinically significant abnormalities on physical examination noted at baseline will be presented as preexisting conditions. New clinically significant abnormalities on study will be presented as AEs.

#### **7.15 12-Lead Electrocardiogram (ECG)**

Results of the 12-lead ECG will be summarized by treatment group using descriptive statistics at baseline and end-of-treatment. The number (n), mean, standard deviation, median, range will be presented. Changes from baseline will also be summarized.

#### **7.16 ECOG Performance Status**

The ECOG PS at baseline and during the treatment period will be presented using frequency counts and percentages for each treatment group.

#### **7.17 Concomitant Medications**

The World Health Organization (WHO) Drug Dictionary will be used to classify concomitant medications by therapeutic class and preferred term. Concomitant medications include medications that started at any time and were taken at any time after the start of treatment until the end of the entire treatment period.

The frequency counts and percentages of subjects in the using different concomitant medications will be tabulated and summarized by treatment group by WHO Drug anatomical therapeutic chemical (ATC) and preferred term. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more preferred terms in the same classification. These data will also be presented in subject listings.

#### **7.18 Interim Analysis**

No formal interim analysis is planned for Phase 2b Monotherapy Expansion and Phase 2b Randomized Phases.

#### **7.19 Safety Review**

Safety analyses will be performed by a vofatamab Safety Oversight Committee (SOC) for Phase 1b, Phase 2 and Phase 2b Monotherapy Expansion and by study-specific Data Monitoring Committee (DMC) for Phase 2b Randomized Phase based on guidelines outlined in the SOC and DMC Charters. The safety review will include AE as well as laboratory and ECG data. The safety assessments for Phase 1b, Phase 2 and Phase 2b Monotherapy Expansion will be conducted in an open fashion.

The safety assessments during the Randomized Phase will be conducted in a blinded fashion on treatment arm and aggregate data. Unblinding in the Randomized Phase will only occur if deemed necessary by the DMC and then only on an individual subject basis.

## **8 SAFETY AND ADVERSE EVENTS**

### **8.1 Definitions**

#### **Adverse Event**

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. Subjects who are discontinued from study drug will be followed for safety outcomes through the safety follow-up visit after the subject's last dose of study drug or until the subject receives another anti-cancer therapy, whichever occurs first.

Suspected Adverse Reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

A life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the investigator or Sponsor, places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **Serious Adverse Event**

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The definition of an SAE also includes any important medical event. Medical and scientific judgment 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 patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be 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.

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

## **8.2 Severity of Adverse Events**

Each AE and SAE should be graded as mild, moderate, severe, life-threatening, or death using the following definitions. The severity of all adverse events will be graded using the NCI CTCAE v4.0 in [Table 5](#).

**Table 5 Adverse Event Severity Grading Scale**

Grade	Severity	Alternate Description <sup>a</sup>
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL <sup>b</sup>
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL <sup>c</sup>
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	

ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.

The NCI CTCAE v4.0 can be found at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_40](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definition of an SAE (see [Section 8.1](#)).

- <sup>a</sup> Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.
- <sup>b</sup> Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- <sup>c</sup> Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious" which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 8.3 Relationship of Adverse Events to Study Drug

The investigator will assess the potential relationship of each AE and SAE to study drug using the following descriptions.

- **Definitely Not Related:** This category applies to an AE or SAE that is clearly not related to the investigational agent/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is

inconsistent with the onset of the event and the exposure to study drug and/or a causal relationship is considered biologically implausible.

- **Unlikely Related:** This category applies to an AE with a temporal relation to administration of the drug which makes a causal relation improbable, and where other drugs, chemicals, or underlying disease provide plausible explanations.
- **Possibly Related:** This category applies to an AE that follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
- **Probably/Likely Related:** This category applies to an AE that is likely related to the investigational agent/procedure. That is, the AE has a reasonable temporal relationship to the administration of the investigational agent(s) or research intervention; is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal
- **Definitely Related:** This category applies to an AE that is certainly related to the investigational agent/procedure. That is, the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, which cannot be explained by concurrent disease or other drugs or chemicals; the response to withdrawal of drug is clinically plausible; and the event has been shown to be definitively pharmacologically or phenomenologically related using a satisfactory rechallenge procedure.

Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

#### 8.4 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). All medical occurrences from the time of signing the informed consent that meet this definition should be recorded. Events preceding first study drug administration, however, should be recorded as medical history, not as AEs.

After initiation of study drug, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study drug, 30 days after subject discontinuation, initiation of another anti-tumor therapy, resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see [Section 8.8](#)).

#### **8.4.1            *Eliciting Adverse Events***

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

“How have you felt since your last clinic visit?”

“Have you had any new or changed health problems since you were last here?”

### **8.5                Recording of Adverse Events**

#### **8.5.1            *Recording Adverse Events on the eCRF***

Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

##### **8.5.1.1            Diagnosis versus Signs and Symptoms**

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

For this study, the NCI CTCAE terms “cytokine release syndrome” or “acute infusion reaction” should not be used. For infusion reactions, each sign and symptom should be recorded as an individual event. If multiple signs or symptoms occur with a given event, each sign or symptom should be recorded separately with its level of severity.

##### **8.5.1.2            Adverse Events Occurring Secondary to Other Events**

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the Adverse Event eCRF.

##### **8.5.1.3            Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

#### 8.5.1.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded as a new entry on the Adverse Event eCRF. If a previously reported SAE increases in severity, it should be reported on the previously submitted eCRF as a follow-up or update and not as a new event.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an Adverse Event eCRF.

#### 8.5.1.5 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the Adverse Event eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin  $5 \times$  the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the Adverse Event eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the Adverse Event eCRF, unless their severity, seriousness, or etiology changes.

#### 8.5.1.6 Worsening of Urothelial Cell Carcinoma

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer, as defined by respective disease criterion or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs, if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

#### 8.5.1.7 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

#### 8.5.1.8 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of UCC will be recorded only on the Study Discontinuation eCRF. All other on study deaths, regardless of attribution, will be recorded on an Adverse Event eCRF and expeditiously reported to the Sponsor.

#### 8.5.1.9 Pregnancy

Conditions of pregnancy and lactation are excluded from study participation. During the course of the study, females of childbearing potential must contact the treating Investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating Investigator).

If an investigator suspects that a subject may be pregnant after the subject started study drug, the study drug or docetaxel, as applicable, must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the subject must be discontinued from the study, and the Investigator must notify the study Sponsor within 24 hours of confirmation.

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of the study drug, a Pregnancy Report eCRF should be completed, printed and faxed to the Sponsor's Drug Safety Department or its designee within 24 hours of learning of the pregnancy, using the fax number listed in [Section 8.6.1](#). Pregnancy should not be recorded on the Adverse Event eCRF.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor. After the study period, such events should still be reported expeditiously to the Sponsor.



Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the investigational product should be classified as serious and recorded on an Adverse Event eCRF and expeditiously reported to the Sponsor during the study period. After the study period, such events should still be reported expeditiously to the Sponsor recorded and reported as an SAE.

In the event the electronic data capture (EDC) system is unavailable, a paper Pregnancy Report Form and Pregnancy Fax Coversheet should be completed and faxed to the Sponsor's Drug Safety Department or its designee at the fax number listed in [Section 8.6.1](#).

## **8.6 Expedited Reporting Requirements for Serious Adverse Events and Serious Drug Reactions**

### **8.6.1 *Reporting Requirements for All SAEs and DLTs***

Investigators will submit reports of all SAEs, regardless of attribution, DLTs, and all protocol-defined non-serious expedited AEs to the Sponsor within 24 hours of learning of the events. For initial SAE, DLT, and protocol-defined non-serious expedited AE reports, investigators should record all case details that can be gathered within 24 hours on an Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Drug Safety Department or its designee by the EDC system. In the event the EDC system is unavailable, a completed SAE paper reporting form and fax coversheet should be faxed immediately upon completion to the Sponsor's Drug Safety Department or its designee at the fax number indicated on the SAE report form. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Investigators will submit written reports of any AEs that meet the definition of a DLT ([Section 5.1.2.1](#)) within 24 hours of learning of the events. Note that the DLT assessment period is from Days 1–21 of Cohort 1.

Real-time safety monitoring will be employed for DLT assessment and dosing modification decisions. During the DLT assessment period this period, investigators must report Grade 3 or 4 AEs (in addition to SAEs) within 24 hours of observing or learning of the events. The Medical Monitor will expeditiously review AEs to determine if they meet the criteria for DLTs ([Section 5.1.2.1](#)).

### **8.6.2 *Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product***

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an Adverse Event eCRF within 24 hours as described in [Section 8.6.1](#).

### **8.6.3** *IRB/EC Notification by the Investigator*

Reports of all SAEs (including follow-up information) must be submitted to the IRB/EC within 10 working days. Copies of each report and documentation of IRB/EC notification and receipt will be kept in the Clinical Investigator's binder. A copy of this notification must be provided to the Sponsor or its designee.

### **8.6.4** *Regulatory Agency Notification by the Sponsor*

The study sponsor or designee shall notify all applicable regulatory agencies by telephone, facsimile transmission, or registration in EudraVigilance database of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the Sponsor's original receipt of the information.

If a previous AE that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the AE in a written report to the appropriate regulatory agencies as soon as possible, but no later than 15 calendar days from the time the determination is made.

## **8.7** **Type and Duration of Follow-Up after Adverse Events**

The investigator should follow all unresolved AEs and SAEs until the events are resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the subject is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate Adverse Event eCRF and in the subject's medical record to facilitate source data verification (SDV) during the study period.

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

## **8.8** **Post-Study Adverse Events**

At the last scheduled visit, the investigator should instruct each subject to report to the investigator any subsequent SAEs that the subject's personal physician believes could be related to prior study treatment.

The investigator should notify the Sponsor of any death or other SAE occurring at any time after a subject has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject who participated in this study. The investigator should report these events to the Sponsor's Drug Safety Department or its designee on the study Adverse Event eCRF. If the study Adverse Event eCRF is not available, the investigator should report the event directly to the Sponsor's Drug Safety Department or its designee.

## **9 STUDY CONDUCT**

### **9.1 Ethics**

#### ***9.1.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)***

The IRB/EC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, the associated informed consent forms, and the informed consent procedures must be submitted to the IRB/EC for review and must be approved before the enrollment of any subject into the study. Investigational Product may not be shipped to the investigator until the Sponsor or its designee has received a copy of the letter or certificate of approval from the IRB/EC for the protocol and any protocol amendments, as applicable.

All subject recruitment and/or advertising information must be submitted to the IRB/EC and the Sponsor or its designee for review and approval prior to implementation. IRB/EC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the IRB/EC should be notified immediately and the amendment forwarded to the IRB/EC for review and approval.

#### ***9.1.2 Ethical Conduct of the Study***

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigator will make every effort that the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the Investigational Product, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

#### ***9.1.3 Informed Consent***

Appropriate forms for documenting written informed consent will be provided by the investigator and reviewed and approved by the Sponsor or its designee before submission to the IRB/EC. The Sponsor or its designee must receive a copy of the IRB/EC's approval of the Informed Consent Form (ICF) before the shipment of Investigational Product to the study site.

It is the investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the conduct of any study procedures. This written informed consent will be obtained after the methods, objectives, requirements, and potential risks of the study have been fully explained to each potential subject. The investigator must explain

to each subject that the subject is completely free to refuse to enter the study or to withdraw from it at any time.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the study that might affect their continued participation in the study. The investigator or a qualified designee will be available to answer each subject's questions throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF.

Receipt of written informed consent will be documented in each potential subject's eCRF. The signed ICF will remain in each subject's study file and must be available to the study monitor(s) at all times.

## **9.2 Regulatory Requirements**

This study will be submitted to the local regulatory authority for approval or notification whichever is applicable. The study will only be undertaken in compliance with the local regulatory requirements.

In accordance with Directive 2001/20/EC, the Sponsor will notify the relevant (European) regulatory authority(ies) and IRBs/ECs within 90 days of the end of the study. If the study terminates early, the Sponsor will notify the relevant (European) regulatory authority(ies) and IRBs/ECs within 15 days and will provide the reasons for early termination.

Safety updates for vofatamab will be prepared by the Sponsor as required, for submission to the relevant regulatory authority(ies).

## **9.3 Investigators and Administrative Structure**

Each investigator must provide the Sponsor and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-investigators listed on Form FDA 1572.

The Sponsor and/or its designee will be responsible for managing and monitoring the clinical study to ensure compliance with FDA and ICH GCP guidelines. A trained designated representative (the monitor) will conduct regular visits to the clinical site, to perform SDV. The monitor will verify the investigator's ongoing qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements.

A Coordinating Investigator will be identified for multicenter studies. The Coordinating Investigator will be selected on the basis of active participation in the study, thorough knowledge of the therapeutic area being studied, and the ability to interpret data. The Coordinating Investigator will read and sign the Clinical Study Report.

## **9.4 Data Handling and Record Keeping**

### **9.4.1 Case Report Forms and Source Documents**

The investigator is required to initiate and maintain, for each subject, an adequate and accurate case history that records all observations and other data related to the study for that subject. A validated EDC system will be used for entry of the data into eCRFs. Data must be recorded on eCRFs approved by the Sponsor or its designee. All information recorded on eCRFs for this study must be consistent with the subject's source documentation.

Initial data entry and any changes to the data will be made only by authorized users, and data entries and changes will be captured in an electronic audit trail. An explanation of any data change should be recorded in the eCRF. All data entered in to the eCRF must be verifiable; therefore, eCRFs will be routinely checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records by the Sponsor or its designee. The investigator must allow direct access to all source documents.

### **9.4.2 Data Quality Assurance**

Monitoring and auditing procedures developed by the Sponsor and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. The Sponsor's designated representative (the monitor) will contact the investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of IRB/EC review, with the stipulation that subject confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting eCRFs and source documents, and ensuring the integrity of the data. Electronic CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other subject records. Instances of missing or uninterruptable data will be resolved in coordination with the investigator.

The monitor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and/or mail. The investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and any and all issues identified by the monitor.

The investigator understands that regulatory authorities, the IRB/EC, and/or the Sponsor or its designees have the right to access all eCRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the

study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

#### **9.4.3            *Records Retention***

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The Investigator/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement. The Sponsor must be notified and will assist with retention should the Investigator/institution be unable to continue maintenance of subject files for the full 15 years. All study records must be stored in a secure and safe facility.

#### **9.4.4            *Disclosure of Source Data and Documents***

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the subject or unless permitted or required by law.

Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Source data/documents generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Sponsor monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

### **9.5                *Subject Confidentiality***

The investigator must ensure that each subject's anonymity is maintained as described below. On the eCRFs or other documents submitted to the Sponsor, subjects must be identified by no more than their initials, date of birth, and a subject number. Signed ICFs and other documents should be kept in strict confidence by the investigator in compliance with applicable regulations and ICH GCP Guidelines. The investigator and institution must permit authorized representatives of the Sponsor, of regulatory agencies, and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The investigator is obligated to inform the subject in the ICF that the above named representatives may review study-related records from subjects.

## **9.6 Procedures for Protocol Amendments**

Any changes to the study, which arise after approval of the protocol, must be documented as protocol amendments. Protocol amendments which are deemed substantial (e.g. affecting the safety of the subject, the scope of the study and/or the scientific quality) will be submitted to regulatory authorities and/or to the IEC/IRB as appropriate. For substantial amendment, the changes will become effective only after approval by the Sponsor, the responsible Investigator, IEC/IRB and competent authorities. All other amendments (i.e. non-substantial or administrative amendments) will be documented in the Trial Master File (TMF).

The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the following:

- IRB/IEC for review and approval/favorable opinion
- Sponsor for agreement
- Regulatory authority(ies), if required

## **9.7 Study Report**

At the conclusion of the study (but within 1 year after study closure), when the data are analyzed, the Sponsor will prepare an integrated Clinical Study Report in compliance with ICH E3. A draft copy of the report will be available for review by the coordinating investigator. The final version will be signed by the Sponsor and the coordinating investigator.

At the conclusion of the study (but within 1 year after study closure), when the data are analyzed, the Sponsor will also post the study results on the European database referred (EudraCT) per Article 11(1) of Directive 2001/20/EC.

## **9.8 Financing and Insurance**

Financing and insurance will be addressed by separate agreements with the study sites.

## **9.9 Publication Policy**

The investigator shall not prepare and/or submit any manuscripts or slide shows based on the Sponsor data for publication or oral presentation prior to the publication of the primary manuscript of the study. The Sponsor shall acknowledge the investigator's contribution to the study in any Sponsor publications regarding the study.

The Sponsor will comply with the requirements for publication of study results and determination of authorship in accordance with standard editorial and ethical practice and with the International Committee of Medical Journal Editors (ICMJE) requirements.

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## 11 SIGNATURE PAGE

Protocol Title: A Dose Escalation, Expansion Study of Vofatamab (B-701) Alone, Plus Docetaxel, or Versus Docetaxel in Subjects with Locally Advanced or Metastatic Urothelial Cell Carcinoma who have Relapsed After, or are Refractory to Standard Therapy

Protocol Number: FIERCE-21 (B-701-U21)

Date of Amendment 6: July 31, 2018  
Date of Amendment 5: July 6, 2017  
Date of Amendment 4: November 21, 2016  
Date of Amendment 3: February 17, 2016  
Date of Amendment 2: December 28, 2015  
Date of Amendment 1: February 24, 2015  
Date of Original Protocol: November 26, 2014

By signing below, I agree to the conditions relating to this study as set out in this protocol (FIERCE-21, B-701-U21, Amendment 6, dated July 31, 2018). I agree to conduct this clinical study according to the International Conference of Harmonisation Guideline on Good Clinical Practice (ICH GCP E6). I fully understand that any changes instituted by me without previous discussion with BioClin Therapeutics, Inc. (BioClin) or their designated representative constitute a violation of the protocol. I agree to adhere to the protocol in all circumstances other than where necessary to protect the well-being of the subject. I will ensure that the study products supplied by BioClin will be used only for administration to subjects included in this study protocol and for no other purpose.

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Investigator Signature

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Date

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Print Name

### Accepted by the Sponsor

As the Sponsor representative, I confirm the Sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the Investigator is informed of all relevant information that becomes available during the conduct of this study.

---

Steve Abella, MD  
Chief Medical Officer  
BioClin Therapeutics Inc.

---

Date

**APPENDIX 1                    EASTERN COOPERATIVE ONCOLOGY GROUP  
PERFORMANCE STATUS SCALE**

<b>Grade</b>	<b>Description</b>
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 housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: [Oken 1982](#).

## **APPENDIX 2            NEW YORK HEART ASSOCIATION CLASSIFICATION OF FUNCTIONAL CARDIAC CAPACITY**

<b>Class</b>	<b>Description</b>
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such subjects are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although subjects are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

## **APPENDIX 3            RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1**

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 ([Eisenhauer 2009](#)) are presented below, with slight modifications and the addition of explanatory text as needed for clarity.

### **Measurability of Tumor at Baseline**

#### **Definitions**

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

#### **a. Measurable Tumor Lesions**

**Tumor Lesions.** Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray.

**Malignant Lymph Nodes.** To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

#### **b. Non-Measurable Tumor Lesions**

Non-measurable tumor lesions encompass small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with short axis  $\geq 10$  but  $< 15$  mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

#### **c. Special Considerations Regarding Lesion Measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

**Bone Lesions:**

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

**Cystic Lesions:**

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

**Lesions with Prior Local Treatment:**

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

**Target Lesions: Specifications by Methods of Measurements**

**a. Measurement of Lesions**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

**b. Method of Assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

**Clinical Lesions.** Clinical lesions will only be considered measurable when they are superficial and  $\geq 10$  mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.



**Chest X-Ray.** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on a chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

**CT, MRI.** CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thicknesses greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. If prior to enrollment it is known that a subject is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the subject at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the subject should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

**Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

**Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology.** The utilization of these techniques for objective tumor evaluation cannot generally be advised.

### **Tumor Response Evaluation**

#### **Assessment of Overall Tumor Burden and Measurable Disease**

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

#### **Baseline Documentation of Target and Non-Target Lesions**

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which subjects have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm  $\times$  30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis  $\geq 10$  mm but  $< 15$  mm) should be considered non-target lesions. Nodes that have a short axis of  $< 10$  mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the electronic Case Report Form (eCRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

## **Response Criteria**

### **a. Evaluation of Target Lesions**

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions  
Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $< 10$  mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline  
In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.  
The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

#### **b. Special Notes on the Assessment of Target Lesions**

**Lymph Nodes.** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

**Target Lesions that Become too Small to Measure.** During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case, BML should not be ticked.

**Lesions that Split or Coalesce on Treatment.** When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

### c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the time points specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

### d. Special Notes on Assessment of Progression of Non-Target Disease

**When the Subject Also Has Measurable Disease.** In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

**When the Subject Has Only Non-Measurable Disease.** This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

## e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject’s baseline lesions show partial or complete response.

For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

## Evaluation of Response

### a. Time Point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs.

Table 6 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline. When subjects have non-measurable (therefore non-target) disease only, Table 7 is to be used.

**Table 6 Time Point Response: Subjects with Target Disease (With or Without Non-Target Lesions)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

**Table 7 Time Point Response: Subjects with Non-Target Disease Only**

<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

<sup>a</sup> “Non-CR/non-PD” is preferred over “stable disease” for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning “stable disease” when no lesions can be measured is not advised.

#### **b. Missing Assessments and Not-Evaluable Designation**

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions, and during the study, only two lesions were assessed but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the subject is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess,” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, as this equates with the case being not evaluable at that time point.

#### **c. Best Overall Response: All Time Points**

The best overall response is determined once all the data for the subject is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient’s best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable at a subsequent time point as specified in the protocol (generally

4 weeks later). In this circumstance, the best overall response can be interpreted as in [Table 8](#).

**Table 8 Best Overall Response When Confirmation of CR and PR required**

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR <sup>a</sup>
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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

#### d. Special Notes of Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which subjects with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.



## **APPENDIX 4            ANAPHYLAXIS PRECAUTIONS AND PROCEDURES**

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice as needed
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape.

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications, as required by subject status and directed by the physician in charge.
5. Continue to observe the subject and document observations.

## APPENDIX 5 PROMIS GLOBAL PHYSICAL HEALTH SHORT SURVEY

	Excellent	Very Good	Good	Fair	Poor
In general, how would you rate your physical health?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	5	4	3	2	1

	Completely	Mostly	Moderately	A little	Not at all
To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	5	4	3	2	1

	None	Mild	Moderate	Severe	Very Severe
How would you rate your fatigue on average?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5

How would you rate your pain on average?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	0	1	2	3	4	5	6	7	8	9	10
	No pain										Worst Imaginable pain

Source: [Hays 2009](#).

## **APPENDIX 6                      INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS**

The following methods of contraception can achieve a failure rate of less than 1% per year when used consistently and correctly, and are considered highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation<sup>1</sup>
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation<sup>1</sup>
  - oral
  - injectable
  - implantable<sup>2</sup>
- Intrauterine device (IUD)<sup>2</sup>
- Intrauterine hormone-releasing system (IUS)<sup>2</sup>
- Bilateral tubal occlusion<sup>2</sup>
- Vasectomized partner<sup>2,3</sup>
- Sexual abstinence<sup>4</sup>

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide<sup>5</sup>
- Cap, diaphragm or sponge with spermicide<sup>5</sup>

<sup>1</sup> Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

<sup>2</sup> Contraception methods that in the context of this guidance are considered to have low user dependency.

<sup>3</sup> Vasectomized partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

<sup>4</sup> In the context of this guidance, 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

<sup>5</sup> A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: [CTFG 2014](#).

## APPENDIX 7 EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ-C30)

ENGLISH



### EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

31									

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

#### During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page



## APPENDIX 8 PHARMACOKINETIC SUB-STUDY

### 1. OBJECTIVES

- To characterize the serum vofatamab concentration in cycle 1, cycle 5 and at steady state for the U21 monotherapy arm.

### 2. RATIONALE

This sub-study will allow a detailed characterization of the PK of vofatamab

### 3. SUB-STUDY DESIGN

Eligible subjects at all centers may be enrolled into the PK sub-study: up to 10 subjects in the monotherapy arm will be enrolled. Subjects have to provide sub-study specific informed consent to participate. A balanced regional and racial distribution is targeted for enrollment.

### 4. ENDPOINT

- Vofatamab serum concentrations before and after vofatamab administration

### 5. ELIGIBILITY

#### • Inclusion

- Subject has provided informed consent for participation in this sub-study. Upon agreement with BioClin Therapeutics, subjects may be consented following Day 1. Back-up samples collected for other testing may be analyzed for any PK timepoint that may have been missed due to later consent.

#### • Exclusion

- Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

### 6. PROCEDURES

Sample collection, handling and storage and general procedures for laboratory assessments relevant for this sub-study are described in Section 6.2.9.

- In the sub-study. PK samples for the assessment of vofatamab will be collected as follows (PK samples collected for all study participants are shown in non-bolded font; additional PK samples required of subjects participating in the PK sub-study are in **bolded** font):
  - Cycle 1
    - Day 1, before vofatamab infusion AND within 30 ( $\pm 15$ ) minutes after completion vofatamab infusion
    - **Day 2 and Day 4**
    - Day 8, before vofatamab infusion AND within 30 ( $\pm 15$ ) minutes after completion vofatamab infusion

- Cycle 2
  - Day 1, before vofatamab infusion AND within 30 ( $\pm$ 15) minutes after completion vofatamab infusion
- **Cycle 3**
  - **Day 1 before vofatamab infusion AND within 30 ( $\pm$ 15) minutes after completion vofatamab infusion**
- Cycle 5
  - Day 1, before vofatamab infusion AND within 30 ( $\pm$ 15) minutes after completion vofatamab infusion
  - **Day 2, Day 8, Day 15, and Day 21**
- **Cycle 6**
  - **Day 1 before vofatamab infusion AND within 30 ( $\pm$ 15) minutes after completion vofatamab infusion**
- Cycle 10
  - Day 1 before vofatamab infusion AND within 30 ( $\pm$ 15) minutes after completion vofatamab infusion
- End of Treatment

## 7. STATISTICAL CONSIDERATIONS

Enrollment of up to 10 subjects represents approximately a 10% sampling of the monotherapy arm and as such is expected to be representative of the overall study population. Statistical methods are described in Section [7.3.1](#)