# A Phase 2, Open-Label, Single-Arm, Multicenter Study to Assess the Safety and Efficacy of ASP1650, a Monoclonal Antibody Targeting Claudin 6 (CLDN6), in Male Subjects with Incurable Platinum Refractory Germ Cell Tumors

## ISN/Protocol 1650-CL-0201

## Version 3.1

## Incorporating Nonsubstantial Amendment 1 [See Section 13]

## 17 April 2020

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Sponsor:

**Astellas Pharma Global Development, Inc. (APGD)**

1 Astellas Way
Northbrook, IL 60062

*Protocol History:*
Version 1.0 [05 Sep 2018]
Version 2.0 [22 Oct 2018]
Version 3.0 [02 Jul 2019]

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# I. SIGNATURES

## 1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 14 Sponsor's Signatures].

## 2. INVESTIGATOR'S SIGNATURE

**A Phase 2, Open-Label, Single-Arm, Multicenter Study to Assess the Safety and Efficacy of ASP1650, a Monoclonal Antibody Targeting Claudin 6 (CLDN6), in Male Subjects with Incurable Platinum Refractory Germ Cell Tumors**

**ISN/Protocol 1650-CL-0201**

**Version 3.1 Incorporating Nonsubstantial Amendment 1**

**17 April 2020**

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

**Principal Investigator:**
Signature: ----------
Date (DD Mmm YYYY)

Printed Name: ---------- ----------
*<Insert name and qualification of the Investigator>*
Address: ----------
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# II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

| | |
|---|---|
| **24-hour Contact for Serious Adverse Events (SAEs)**<br>See [Section 5.5.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email | **Please fax or email the SAE Worksheet to:**<br>**Astellas Pharma Global Development, Inc.**<br>**Pharmacovigilance**<br>**North America Fax Number: 888-396-3750**<br>**North America Alternate Fax: 847-317-1241**<br>**Email: safety-us@astellas.com** |
| Medical Monitor/Study Physician: | PPD, Development Medical Science – Oncology<br>Astellas Pharma Global Development, Inc.<br>1 Astellas Way, Northbrook, Illinois 60062<br>PPD |
| Clinical Research Contacts: | PPD<br>Astellas Pharma Global Development, Inc.<br>1 Astellas Way, Northbrook, Illinois 60062<br>PPD |

# III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

## List of Abbreviations

| Abbreviations | Description of abbreviations |
|---|---|
| 3xW | three times a week |
| ADCC | antibody-dependent cell-mediated cytotoxicity |
| AE | adverse event |
| AFP | alpha-fetoprotein |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AT | aminotransferases |
| AUC | area under the concentration-time curve |
| βhCG | beta human chorionic gonadotropin |
| BOIN | Bayesian Optimal Interval |
| C1D1 | cycle 1/day 1 |
| CAs | Competent Authorities |
| CBR | clinical benefit rate |
| CDC | complement-dependent cytotoxicity |
| cEC | concerned Ethics Committee |
| CIOMS | council for international organizations of medical sciences |
| CLDN6 | Claudin 6 |
| $C_{max}$ | maximum concentration |
| $C_{trough}$ | concentration immediately prior to dosing at multiple dosing |
| CNS | central nervous system |
| CR | complete response |
| CRO | contract research organization |
| CT | computed tomography |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| DEAS | dose limiting toxicity evaluation analysis set |
| DEC | Dose Evaluation Committee |
| DLT | dose limiting toxicity |
| DPD | Data Protection Directive |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| FAS | full analysis set |
| FFPE | formalin fixed paraffin embedded |
| FIH | first-in-human |
| GCP | Good Clinical Practice |
| GCT | germ-cell tumor |
| GMP | Good Manufacturing Practice |
| HBcAb | hepatitis B core antibody |

| Abbreviations | Description of abbreviations |
|---|---|
| HBsAg | hepatitis B antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| IRT | interactive response technology |
| ISN | international study number |
| LA-CRF | liver abnormality case report form |
| LFT | liver function tests |
| LH | luteinizing hormone |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI-CTCAE | National Cancer Institute Common Toxicity Criteria for Adverse Events |
| ORR | objective response rate |
| PBSCT | peripheral-blood stem-cell transplant |
| PD | progressive disease |
| PGx | pharmacogenomics |
| PFS | progression-free survival |
| Ph. Eur. | European Pharmacopoeia |
| PKAS | pharmacokinetic analysis set |
| PPS | per protocol set |
| PR | partial response |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| QA | quality assurance |
| QC | quality control |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | ribonucleic acid |
| RP2D | recommended phase 2 dose |
| RSI | reference safety information |
| SAE | serious adverse event |

| Abbreviations | Description of abbreviations |
|---|---|
| SAF | safety analysis set |
| SAP | Statistical Analysis Plan |
| SD | stable disease |
| SOP | standard operating procedure |
| stage I | Simon Stage I |
| stage II | Simon Stage II |
| SUSAR | suspected unexpected serious adverse reaction |
| T4 | thyroxine |
| TSH | thyroid stimulating hormone |
| TEAE | treatment-emergent adverse event |
| $t_{max}$ | time of maximum concentration |
| ULN | upper limit of normal |
| USM | Urgent Safety Measure |

## Definition of Key Study Terms

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

# IV. SYNOPSIS

| | |
|---|---|
| **Date and Version No of Protocol Synopsis:** | 17 April, Version 3.1 |
| **Sponsor:**<br>Astellas Pharma Global Development Inc. (APGD) | **Protocol Number:**<br>1650-CL-0201 |
| **Name of Study Drug:**<br>ASP1650 (IMAB027) | **Phase of Development:**<br>Phase 2 |
| **Title of Study:**<br>A Phase 2, Open-Label, Single-Arm, Multicenter Study to Assess the Safety and Efficacy of ASP1650, a Monoclonal Antibody Targeting Claudin 6 (CLDN6), in Male Subjects with Incurable Platinum Refractory Germ Cell Tumors | |
| **Planned Study Period:**<br>From 1Q2019 to 3Q2022 | |
| **Study Objective(s):**<br>Primary:<br>• To establish the recommended phase 2 dose (RP2D) of ASP1650 in subjects with incurable platinum refractory germ cell tumors (Safety Lead-in Phase)<br>• To evaluate the efficacy of ASP1650 as measured by confirmed objective response rate (ORR), as assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (RECIST v1.1 and serum tumor biomarker [beta human chorionic gonadotropin [βhCG] and alpha-fetoprotein [AFP] response criteria) in subjects with incurable platinum refractory germ cell tumors (phase 2)<br>Secondary:<br>• To evaluate the following efficacy measures:<br>o Confirmed ORR RECIST v1.1<br>o Clinical benefit rate (CBR), as assessed by modified RECIST v1.1 and RECIST v1.1<br>o Duration of response, as assessed by the modified RECIST v1.1 and RECIST v1.1<br>o Progression-free survival (PFS), as assessed by modified RECIST v1.1 and RECIST v1.1<br>• To evaluate safety and tolerability of ASP1650<br>• To evaluate the effect of ASP1650 on changes in serum βhCG and AFP<br>• To evaluate the pharmacokinetics of ASP1650<br>Exploratory:<br>• To evaluate the immunogenicity profile of ASP1650<br>• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome to ASP1650 | |
| **Planned Total Number of Study Centers and Location(s):**<br>Approximately 4 centers in the United States | |
| **Study Population:**<br>Male subjects with incurable platinum refractory germ cell tumors for whom no standard of care treatment exists or who are ineligible to receive available standard of care treatment based on investigator's clinical judgment. | |

**Number of Subjects to be Enrolled:**

Up to 46 subjects
Safety Lead-in: 9 to 18 subjects
Simon Stage I (stage I): 13 subjects (including subjects from the RP2D cohort of the Safety-Lead in Phase)
Simon Stage II (stage II): 21 subjects

**Study Design Overview:**

This is a phase 2, open-label, single-arm, multicenter study to assess the safety and efficacy of ASP1650, a monoclonal antibody (mAb) targeting CLDN6, in male subjects with incurable platinum refractory germ cell tumors.

The study consists of 2 phases: Safety Lead-in phase and phase 2. For all subjects, the study will consist of the following periods: Screening, Enrollment, Treatment and Follow-up. Each subject may complete a maximum of 12 treatment cycles. One treatment cycle is 14 days. After discontinuation of study drug treatment, all subjects will complete a study treatment discontinuation visit and a safety follow-up visit.

**Screening and Enrollment Period**

Screening will take place up to 45 days prior to enrollment. Re-screening may be allowed 1 time per subject upon discussion with the medical monitor.

**Treatment Period**

*Safety Lead-in Phase*

The Safety Lead-in phase of this study is to establish the tolerability of RP2D (ASP1650 1500 mg/m$^2$ once every 2 weeks [Q2W]). An initial dose level of ASP1650 1000 mg/m$^2$ Q2W will be evaluated in a 3-subject cohort (cohort 1), and if well tolerated, a new subject cohort (minimum 3 and up to 4 subjects) will be opened to evaluate a dose level of ASP1650 1500 mg/m$^2$ Q2W (cohort 2) according to the Bayesian Optimal Interval (BOIN) Design. [Liu et al, 2015]. Based on tolerability observed in cohort 2, an additional subject cohort (cohort 3) will be opened to evaluate 1500 mg/m$^2$ Q2W (minimum 3 and up to 4 subjects) or de-escalation to 1250 mg/m$^2$ Q2W if 1500 mg/m$^2$ Q2W is not tolerable (minimum 6 and up to 8 subjects). Nine to 18 subjects will be enrolled in the Safety Lead-in phase. The RP2D determination will be based on at least 6 evaluable subjects at the RP2D as determined by the Dose Evaluation Committee (DEC).

There will be at least 3 calendar days between the treatment initiation of the first subject and treatment initiation of all subsequent subjects at the same dose level.

The dose limiting toxicity (DLT) observation period will be from cycle 1/day 1 (C1D1) through C2D14. Evaluable subjects are defined as subjects who experience a DLT or in the absence of DLT, complete the DLT observation period. Subjects who are later discovered not to meet eligibility criteria or are not evaluable for DLT may be replaced. If no DLTs are observed in the first 6 evaluable subjects (cohorts 1 and 2), the DLT observation period for cohort 3 may be reduced to ClD1 through C1D14 (one cycle).

**Study Design Overview continued:**

Dose evaluation rules based on the BOIN design with target DLT rate of 0.30 and optimal interval of (0.236, 0.359) are as follows:

| | **Number of Subjects Treated at Current Dose Level** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Action** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Escalate dose if number of subjects with DLT ≤ | 0 | 0 | 1 | 1 | 1 | 1 | 2 |
| Stay at current dose level if number of subjects with DLT = | 1 | 1 | - | 2 | 2 | 2 | 3 |
| De-escalate if number of subjects with DLT = | 2* | 2 | 2 or 3 | 3 | 3 or 4 | 3 or 4 | 4 |
| Stop if number of subjects with DLT ≥ | 3 | 3 | 4 | 4 | 5 | 5 | 5 |

DLT: dose limiting toxicity.

* The study may be terminated instead of de-escalation upon discussion with DEC.

The DEC will be responsible for the review of individual subject safety data in order to provide an assessment of whether reduction or escalation should occur within the next cohort and/or to determine when maximum tolerated dose has been reached in a given dose level. Additional details regarding responsibilities and membership requirements will be included in the DEC Charter.

**Proposed Dose Levels of ASP1650**

| **Dose Level** | **ASP1650** | **Planned Number of Subjects** |
|---|---|---|
| 1 | 1000 mg/m$^2$ | 3 |
| 2 | 1500 mg/m$^2$ | 6-8 |
| De-escalated | 1250 mg/m$^2$ | Only if necessary based on DLTs of Dose Level 2 |

DLT: dose limiting toxicity

At minimum, safety data from the DLT observation period are needed for the DEC meeting; however, all available safety findings, including those occurring after the designated DLT observation period that meet DLT criteria ("delayed DLT"), will be considered.

Subjects who are tolerating study drug at a dose level concurrently under review due to DLTs in another subject are allowed to continue dosing through week 24, as tolerated unless otherwise directed by the DEC.

Enrollment of 3 subjects at the target RP2D (1500 mg/m$^2$ Q2W) will begin once the 1000 mg/m$^2$ Q2W dose level has been deemed tolerable. A de-escalation dose cohort will be opened at 1250 mg/m$^2$ Q2W if 1500 mg/m$^2$ Q2W has been deemed not tolerable. Subjects enrolled in the 1000 mg/m$^2$ Q2W dose level will continue treatment at that dose level (unless they meet study treatment discontinuation criteria) and will be dose escalated to the RP2D after the RP2D is deemed tolerable.

*Dose Limiting Toxicity Criteria*

A DLT is defined as any of the following adverse events (AEs; graded using National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] version 5.0) or laboratory findings that the investigator (or sponsor) cannot clearly attribute to a cause other than study drug:

- Grade 4 neutropenia or grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia; or grade 3 thrombocytopenia accompanied by bleeding that requires any transfusion

- Grade 4 anemia or grade 3 anemia requiring transfusion
- Grade ≥ 3 non-hematological AE
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN; grade ≥ 3) without liver metastases
- AST or ALT > 8 x ULN in subjects with liver metastases
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN (in subject with Gilbert syndrome: AST or ALT > 3 x ULN and **direct** bilirubin > 1.5 x ULN)
- Total bilirubin > 3 x ULN (grade ≥ 3)
- Amylase or lipase > 2 x ULN (grade ≥ 3)
- Infusion-related reaction (IRR) that requires the infusion to be permanently discontinued

**Phase 2**

Once RP2D has been established as tolerable, up to 34 subjects will be enrolled in phase 2 to receive ASP1650 Q2W starting on C1D1 for up to a maximum of 12 cycles or until a study discontinuation criteria has been met, whichever occurs earlier.

A Simon's 2-stage design is implemented to allow for early termination. In stage I, a total of 13 subjects will be enrolled including the subjects from the RP2D cohort of the Safety Lead-in phase will be evaluated for response. If there is 1 or fewer responses among these 13 subjects, the study will be stopped early. Otherwise, an additional 21 subjects will be enrolled in stage II.

*Safety Lead-in and Phase 2 Assessments*

Radiologic disease assessment will be evaluated every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks ± 7 days thereafter until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment, whichever comes earlier. All measurable disease must be documented at Screening and re-assessed at each subsequent radiologic evaluation. Imaging will include computed tomography (CT) scans with contrast of the thorax, abdomen and pelvis. If the CT scan with contrast is medically not feasible, a CT scan without contrast or magnetic resonance imaging may be used for imaging. Bone scans (or focal X-ray) or brain imaging may be performed if metastatic disease is suspected. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change.

Blood will be drawn for the measurement of serum AFP and serum βhCG at day 1 of every cycle and during the post treatment period follow up period to align with imaging assessment (every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks ± 7 days thereafter) until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment.

Response assessments for the primary objective of this trial (ORR) will be made using modified RECIST v1.1. The same measurable and non-measurable lesions determined at baseline will be followed at subsequent timepoints according to RECIST v1.1. Response assessments by RECIST v1.1 and modified RECIST v1.1 will be based upon local investigator evaluation.

*Safety Assessments*

Safety assessments will include AEs, vital signs, electrocardiograms (ECGs), physical exams, Eastern Cooperative Oncology Group (ECOG) performance status and laboratory assessments. Severity of AEs and laboratory abnormalities will be assessed based on NCI-CTCAE.

*Biomarkers and Other Sampling*

An archival tumor specimen will be collected prior to first dose of study treatment. If archival tissue is unavailable or insufficient, a tumor biopsy may be performed during the screening period if the subject is an appropriate candidate for tumor biopsy.

Samples for pharmacokinetics, immunogenicity and biomarkers will be collected. An optional on treatment tumor tissue sample may be collected. Pharmacogenomics and post-progression tumor samples may be collected for those subjects who sign separate informed consent forms.

**Follow-up Period**

Following discontinuation from study treatment, subjects will have a Study Treatment Discontinuation Visit ≤ 7 days after their last dose of study drug or decision by the investigator to discontinue treatment, in addition to a Safety Follow-up visit at 30 days (+7 days) after their last dose of study drug.

If a subject discontinues study drug prior to radiologic progression, the subject should enter the Post-Treatment Follow-up Period. The subject should continue to undergo imaging assessments and serum AFP and serum βhCG every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks ± 7 days thereafter until 1 of the following events occurs:

- Radiological disease progression
- Subject starts another anticancer treatment

All post-progression anti-cancer therapies including date and site of progression will be recorded on the electronic case report form.

**Inclusion/Exclusion Criteria:**

*Inclusion Criteria:*

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

*General Criteria:*

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject or legally authorized representative (if applicable) prior to any study-related procedures.
2. Subject is male and considered an adult (e.g., ≥ 18 years of age in the US) according to local regulation at the time of signing the informed consent.
3. A male subject with female partner(s) of childbearing potential must agree to use contraception as detailed in Appendix 12.3 Contraception Requirements during the treatment period and for at least 6 months after the final study drug administration.
4. Subject must not donate sperm during the treatment period and for 6 months after the final study treatment administration.
5. A male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 6 months after the final study treatment administration.
6. Subject agrees not to participate in another interventional study while receiving study drug in present study.

*Disease Specific Criteria:*

7. Subject has histological evidence of germ cell tumor. Subjects with seminoma and nonseminoma are eligible.
8. Subject must have a germ cell tumor that is not amenable to cure with either surgery or chemotherapy.
9. Subject must have received initial cisplatin based combination chemotherapy AND demonstrated progression following at least 1 salvage regimen for advanced germ cell neoplasm (including relapsed primary mediastinal nonseminomatous germ cell tumor).
    - Initial cisplatin based combination therapy includes bleomycin-etoposide-cisplatin, cisplatin-etoposide, etoposide-ifosfamide-cisplatin or similar regimens
    - "Salvage" regimens include high dose chemotherapy, paclitaxel-ifosfamide-cisplatin, vinblastine-ifosfamide-cisplatin or similar regimens
    - "Failure" of prior therapy is defined as:
        - A > 25% increase in the products of perpendicular diameters of measurable tumor masses during prior therapy, which are not amenable to surgical resection; OR
        - The presence of new tumor that are not amenable to surgical resection; OR
        - An increase in AFP or βhCG (≥ 50% increase in 2 separate samples collected at least 1 week apart are required if rising tumor markers are the only evidence of failure).

          NOTE: Subjects with clinically growing teratoma (enlarging mature teratoma arising during or after chemotherapy for a non-seminomatous germ-cell tumor and with normal serum levels of AFP and βhCG) should undergo surgical resection if feasible.
10. Subjects with late relapse (> 2 years) not amenable to resection are eligible.
11. Subjects must have evidence of recurrent or metastatic carcinoma by 1 or more of the following:
    - Subject has measurable disease according to RECIST v1.1 within 28 days prior to the first dose of study treatment. For subjects with only 1 measurable lesion and prior radiotherapy, the lesion must be outside the field of prior radiotherapy or must have documented progression following radiation therapy.
    - Subject has a baseline rising tumor marker (AFP or βhCG).

NOTE: If a rising tumor marker is the only evidence of progressive disease, at least 2 consecutive rising values at least 1 week apart are needed. Subjects with only evidence of disease as rising tumor marker AFP and βhCG will be assessed for alternate causes of increased serum levels of these markers, such as cross reaction with luteinizing hormone (LH) (can be tested if needed by testosterone suppression of LH), hepatitis, use of marijuana or second primary tumor.

*Physical or Laboratory Findings*

12. Subject must have an available tumor specimen in a tissue block or unstained serial slides, or subject is an appropriate candidate for tumor biopsy as determined by the investigator and is amenable to undergoing a tumor biopsy during the screening period.
13. Subject has ECOG performance status of 0 to 2.
14. Subject must meet all of the following criteria based on the centrally analyzed laboratory tests within 14 days prior to the first dose of study treatment. If repeat screening labs are required, local laboratory results can be used to confirm eligibility. In case of multiple central laboratory data within this period, the most recent data should be used to determine eligibility.
    - Hemoglobin ≥ 8 g/dL
    - Absolute neutrophil count ≥ 1.0 x $10^9$/L
    - Platelets ≥ 75 x $10^9$/L
    - Albumin ≥ 2.5 g/dL

- Total bilirubin ≤ 2 x ULN or direct bilirubin ≤ ULN for subjects with total bilirubin levels > 2 x ULN
- AST and ALT ≤ 2.5 x ULN without liver metastases (or ≤ 5 x ULN if liver metastases are present)
- Estimated glomerular filtration rate ≥ 30 mL/min/1.73 $m^2$
- Prothrombin time/international normalized ratio and partial thromboplastin time (PTT) ≤ 2 x ULN (except for subjects receiving anticoagulation therapy)

***Exclusion Criteria:***

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

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

*Prohibited Treatment or Therapies*

1. Subject has received systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to first dose of study treatment. Subject using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone) or a single dose of systemic corticosteroids is eligible. Subject who received systemic steroids for asymptomatic CNS metastases within 14 days prior to first dose of study treatment is eligible.
2. Subject has received other investigational agents or devices within 28 days prior to first dose of study treatment.
3. Subject has had a prior anti-cancer mAb within 4 weeks prior to study day 1 or has not recovered (i.e., ≤ grade 1 or at baseline) from AE due to mAb agents administered more than 4 weeks earlier.
4. Subject has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or has not recovered (i.e., ≤ grade 2 or at baseline) from AEs due to a previously administered agent.

*Medical History or Concurrent Disease*

5. Subject has prior severe allergic reaction or intolerance to an mAb, including humanized or chimeric antibodies that required permanent discontinuation.
6. Subject has known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment.
7. Subject has an active human immunodeficiency virus (HIV) infection or known active hepatitis B (HBsAg) or C infection. Subjects with well-controlled HIV infections (i.e., without detectable viral load) are eligible. For subjects who are negative for HBsAg, but HBcAb positive, an HBsAg DNA test will be performed and if positive, the subject will be excluded. Subjects with positive serology but negative hepatitis C virus (HCV) RNA test results are eligible.
8. This criterion has been removed.
9. Subject has active infection requiring systemic therapy that has not completely resolved within 14 days prior to first dose of study treatment.
10. Subject has symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Subject with asymptomatic CNS metastases is eligible.
11. Subject has had a major surgical procedure and has not completely recovered within 28 days prior to the first dose of study treatment.

12. Subject has psychiatric illness or social situations that would preclude study compliance, per investigator's judgment.
13. Subject has another malignancy for which treatment is required per investigator's clinical judgment. Subject with negligible risk of metastasis or death per investigator's clinical judgment is eligible (e.g., basal or squamous cell skin cancer, localized prostate cancer treated with curative intent or incidental prostate cancer T1-T2a, Gleeson $\leq 3 + 4$, PSA $\leq 0.5$ and who are undergoing active surveillance).
14. Subject has any concurrent disease, infection, or co-morbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.

**Investigational Product(s):**

| | |
|---|---|
| **ASP1650:** | The investigational product, ASP1650, is a sterile lyophilized powder preparation with the chimeric mAb ASP1650 as the active pharmaceutical ingredient.<br>Each vial contains 200 mg of ASP1650 and has to be reconstituted with 4.4 mL sterile water for injection to a concentration of 45 mg/mL. Further dilution with sterile 5% Dextrose Injection, USP to a final concentration of 2 to 25 mg/mL is required. |
| **Dose(s):** | **Dose Level 1:** 1000 mg/m$^2$ Q2W<br>**Dose Level 2:** 1500 mg/m$^2$ Q2W<br>**De-escalation Dose:** 1250 mg/m$^2$ Q2W |
| **Dosing Schedule:** | Subjects will be treated with ASP1650 on day 1 of each cycle (each cycle has 14 days). All subjects will be treated for a maximum of 12 cycles or until the subject meets study treatment discontinuation criteria. |
| **Mode of Administration:** | The investigational product is administered intravenously. The 1000 mg/m$^2$ Q2W dose is administered as a 2-hour infusion and the 1250 mg/m$^2$ Q2W and 1500 mg/m$^2$ Q2W doses are administered as a 3-hour infusion, all of which may be interrupted or slowed down to manage toxicity. The infusion of ASP1650 should be completed in less than 6 hours from the start of infusion. |

Q2W: every 2 weeks

**Concomitant Medication Restrictions or Requirements:**

*Prohibited Concomitant Treatment*

The following are strictly prohibited:

- Systemic immunosuppressive agents:
  - Concurrent systemic immunosuppressive therapy, in particular systemic corticosteroids, must be stopped 14 days prior to first dose of study treatment. Subjects are allowed to initiate systemic steroids for CNS metastases after first dose of study treatment.
    - Subjects are allowed to use a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone) or a single dose of systemic corticosteroids.
- Other systemic chemotherapy, immunotherapy, radiotherapy, herbal medications or other treatments intended for antitumor activity. Palliative radiotherapy for peripheral bone metastases is allowed.
- Investigational products or therapy other than ASP1650.

*Cautionary Concomitant Treatment*

Considerations should be given to avoid or minimize the use of the following concomitant medications, if possible, during ASP1650 treatment:

- Systemic corticosteroids, because their impact on the potential efficacy of ASP1650 is not known.
  - Systemic corticosteroids should be avoided or minimized while subject is on study treatment unless required for management of an emergent medical condition (e.g., severe hypersensitivity reaction).
  - For a subject's first dose of ASP1650, it is recommended that the prophylactic use of corticosteroids be avoided.
  - Inhaled, intranasal and topically applied steroids are allowed.

*Prohibited Non-drug Procedures*

- Any surgery (including palliative) that involves removal of tumor/metastases masses that may affect the efficacy assessments (removal of small non-measurable masses may be allowed upon discussion with the medical monitor)

**Duration of Treatment:**

Subjects will receive ASP1650 for up to a maximum of 12 treatment cycles or until disease progression, toxicity requiring study treatment cessation, start of another anticancer treatment, or other study discontinuation criteria are met.

**Study Treatment Discontinuation Criteria:**

The study treatment period is a maximum of 12 treatment cycles. A subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The subject will be discontinued from study treatment if any of the following occur:

- Investigator determines it is in the subject's best interest to discontinue study treatment.
- Subject develops disease progression based on serum tumor markers or radiological disease progression as assessed by the investigator.
  - If the investigator believes that the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study treatment up to a maximum of 12 treatment cycles.
- Subject starts another systemic chemotherapy, immunotherapy, radiotherapy or other treatment intended for antitumor activity.
- Subject starts other investigational agent or device.
- Subject develops unacceptable toxicity.
- Subject has a delay of study treatment for ≥ 28 days from when the next study treatment was scheduled to be administered. However, restarting study treatment after dosing delay (beyond ≥ 28 days from when the next study treatment was scheduled to be administered) may be allowed based on investigator consultation with, and approval of, the Astellas medical monitor.
- Subject develops inter-current illness that the investigator determines may jeopardize the subject's safety if the subject continues to receive study treatment.
- Significant deviation from the protocol or eligibility criteria as determined by the sponsor.
- Subject declines further treatment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject is noncompliant with the protocol based on investigator or medical monitor assessment.

NOTE: If a subject discontinues ASP1650 prior to disease progression per modified RECIST v1.1 and is not receiving any other systemic anti-cancer therapy, the subject must continue to undergo radiological assessments per protocol-specified schedule.

**Study Discontinuation Criteria**

A subject will be discontinued from the study if any of the following occur:

- Subject or legally authorized representative specifically withdraws consent for any further contact.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death (from any cause).
- Study termination by the sponsor.

**Endpoints for Evaluation:**

**Primary:**

- Establish RP2D of ASP1650 through DLT assessment by DEC
- Confirmed ORR, defined as the proportion of subjects who have a best overall response of confirmed CR or confirmed partial response (PR), as assessed by modified RECIST v1.1.

**Secondary:**

- Safety and tolerability, as measured by AEs, laboratory test results, vital signs, ECGs and ECOG performance status
- ORR by RECIST v1.1
- CBR, as assessed by modified RECIST v1.1 and RECIST v1.1
- Duration of response, as assessed by modified RECIST v1.1 and RECIST v1.1
- PFS, as assessed by modified RECIST v1.1 and RECIST v1.1
- Percent change in serum βhCG and AFP
- Pharmacokinetics of ASP1650 ($AUC_{336}$, $C_{max}$, $t_{max,}$ $C_{trough)}$

**Exploratory:**

- Immunogenicity of ASP1650 as measured by the frequency of antidrug antibody positive subjects
- Potential genomic and/or other exploratory biomarkers that may be related to treatment outcome of ASP1650

**Statistical Methods:**

**Sample Size Justification:**

The sample size for the Safety Lead-in Phase is not based on a statistical power calculation. The planned number of up to 18 subjects would provide adequate information for the objectives of the safety cohort.

Simon's optimal 2-stage design [Simon, 1989] will be used for conducting phase 2 of the study. The null hypothesis is that the true ORR is 10%, and the alternative hypothesis is that the true ORR is 25%. The study will be carried out in 2 stages. In stage I, a total number of 13 subjects treated at the RP2D will be evaluated.

If there are 1 or fewer responses among these 13 subjects, the study will be stopped early for futility. Otherwise, an additional 21 subjects will be enrolled in stage II, resulting in a total number sample size of 34. If there are 6 or more responses among these 34 subjects, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 10% and yields the power of 80%.

**Analysis Populations:**

- The full analysis set (FAS) will include all enrolled subjects.
- The per-protocol set (PPS) will consist of the subset of the FAS who do not meet PPS exclusion criteria. These criteria are intended to capture relevant non-adherence to the protocol and will be defined in the Statistical Analysis Plan (SAP).
- The safety analysis set (SAF) will contain all subjects who received at least 1 dose of study drug. The SAF will be used for all safety analyses.
- The pharmacokinetic analysis set (PKAS) will consist of the subset of the SAF for which at least 1 ASP1650 concentration measurement is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. The PKAS will be used for description of pharmacokinetic data.
- The dose limiting toxicity evaluation analysis set (DEAS) is defined as all subjects in SAF by excluding the subjects who meet the following criterion:
    - A subject without a DLT who receives less than the planned ASP1650 dose during the DLT observation period.
- DEAS will be used for the analysis of DLT data.

**Efficacy Analyses:**

All efficacy analyses will be performed using FAS. In addition, PPS will be used for the primary and key secondary efficacy analyses.

**Safety Analyses:**

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

All summaries of AEs will include only treatment-emergent events unless otherwise stated. AEs will be categorized by System Organ Class and preferred term using MedDRA and will be graded for severity according to the NCI-CTCAE.

**Pharmacokinetics:**

Descriptive statistics will be used to summarize serum concentrations and pharmacokinetic parameters of ASP1650 by dose. The potential relationship between ASP1650 immunogenicity and ASP1650 pharmacokinetics, efficacy and safety profile will be assessed. Additional model-based analyses may be performed and reported separately.

**Biomarkers:**

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

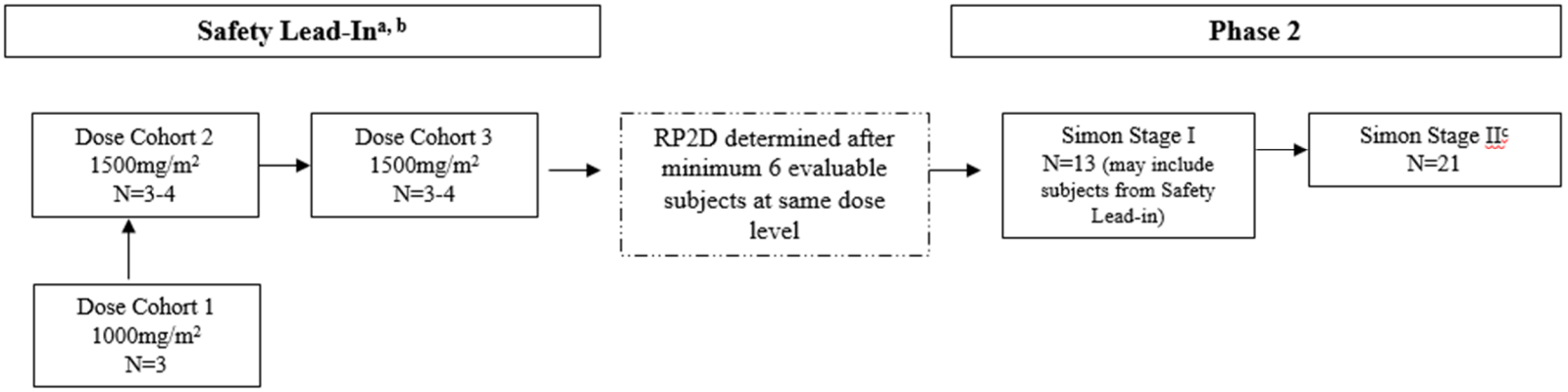
**Interim Analyses:**

No formal interim analysis is planned during the Safety Lead-in phase. Safety, pharmacokinetic and other clinical data will be reviewed on an ongoing basis.

A futility analysis will be conducted 24 weeks after the first dose of the 13$^{th}$ subject in stage I of phase 2 of the study. The study may be stopped if less than 2 confirmed response (confirmed CR or confirmed PR by modified RECIST v1.1) are observed.

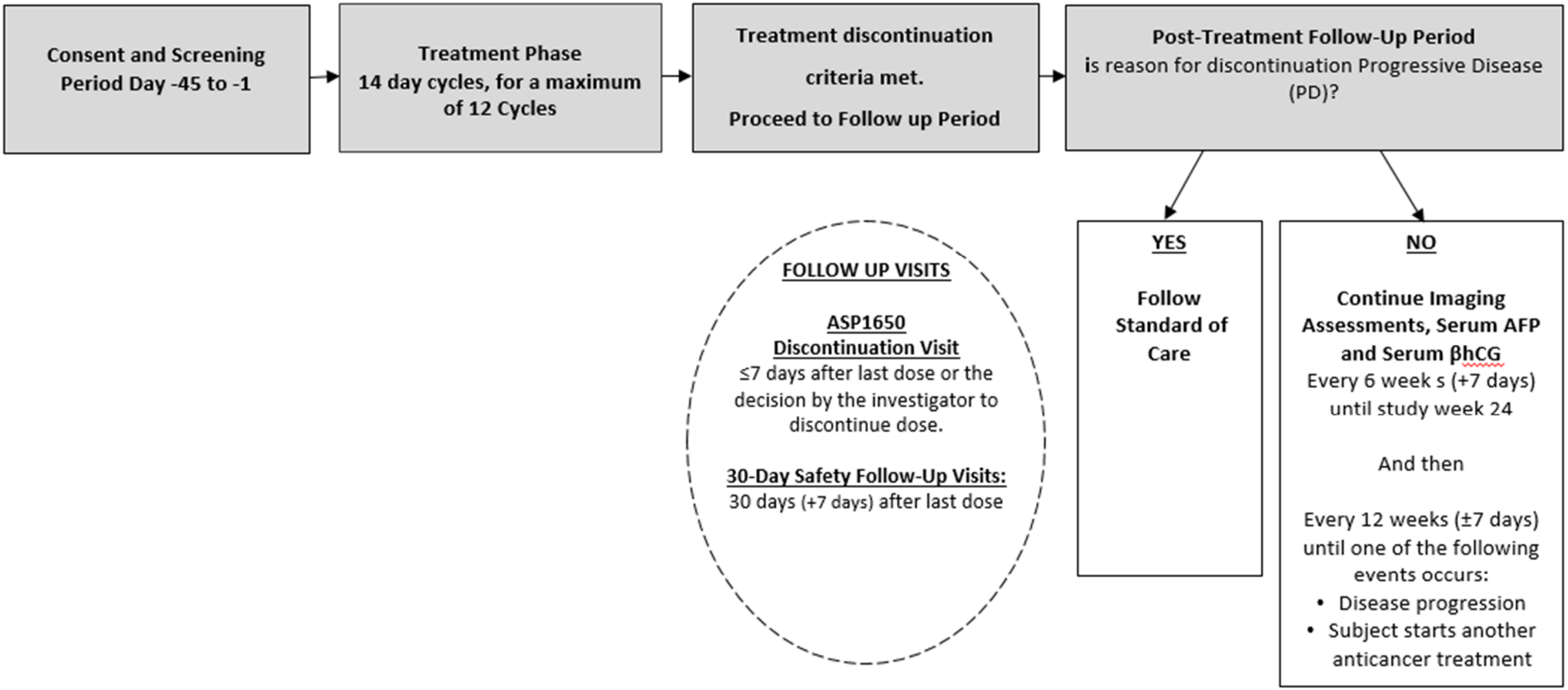
# V. STUDY SCHEMATIC, FLOW CHART AND SCHEDULE OF ASSESSMENTS

## Study Schematic




a. Proposed dose escalation levels. Actual dose escalation cohorts to be determined based on DLT review by DEC.
b. DLT observation period is 2 cycles (C1D1 through C2D14). If no DLTs are observed in the first 6 evaluable subjects the observation period may be shortened to 1 cycle (C1D1 through C1D14)
c. Stage II will be initiated if ≥ 2 responses observed in Stage I

## Study Flow Chart



## Table 1 Schedule of Assessments

| VISIT | Screening[1] | Study Treatment Period (Each Cycle = 14 Days) | | Follow-up | |
|---|---|---|---|---|---|
| | | Cycles 1 to 12[2] | | Study Treatment Discontinuation Visit[3] | 30-Day Safety Follow-up Visit[4] |
| Day | | 1 | 2 to 14 | ≤ 7 days from date of last dose or investigator decision to discontinue dose | 30 days from date of last dose |
| Visit Window (business days) | -45 to -1 | +5* | (no visit) | 0 | +7 |
| Informed Consent | X | | | | |
| Tumor Sample[5] | X | | | | |
| Optional Tumor Tissue Sample Biopsy (if applicable)[6] | | X | | | |
| Medical and Disease History | X | | | | |
| Confirmation of Inclusion/Exclusion Criteria[7] | X | X | | | |
| Enrollment[8] | | X | | | |
| ASP1650 Administration[9] | | X | | | |
| Post-infusion Observation Period[10] | | X | | | |
| Glucose Finger Prick[11] | | X | For diabetic subjects, as clinically indicated. | | |
| Physical Examination[12] | X | X | | X | X |
| Weight[12] | X | X | | X | X |
| ECOG Performance Status[12] | X | X | | X | |
| Vital Signs[13] | X | X | | X | X |
| 12-lead ECG[14] | X | If clinically indicated and/or per local requirements | | X | X |

*Table continued on next page*

| VISIT | Screening[1] | Study Treatment Period (Each Cycle = 14 Days) | | Follow-up | |
|---|---|---|---|---|---|
| | | Cycles 1 to 12[2] | | Study Treatment Discontinuation Visit[3] | 30-Day Safety Follow-up Visit[4] |
| **Day** | | **1** | **2 to 14** | **≤ 7 days from date of last dose or investigator decision to discontinue dose** | **30 days from date of last dose** |
| Visit Window (business days) | -45 to -1 | +5* | (no visit) | 0 | +7 |
| Image Assessment[15] | **X** | **Every 6 weeks (+ 7 days) counting from C1D1 for the first 24 weeks, and then every 12 weeks (± 7 days) until subject develops radiographic disease by RECIST v1.1 or starts other systemic anticancer therapy** | | | |
| Clinical Safety Labs[16] | X | X | | X | X |
| Thyroid Function Test (TSH, T4)[17] | | X | If clinically indicated | X | |
| Coagulation Parameters (PT, PTT and INR)[18] | X | If clinically indicated | | X | |
| Pharmacokinetics of ASP1650 (Serum) | See Table 2 below for sample collection schedule | | | | |
| Antidrug Antibodies (ADA) for Immunogenicity | See Table 2 below for sample collection schedule | | | | |
| Exploratory Biomarkers (Serum)[19] | | X | | X | |
| Exploratory Biomarkers (Plasma)[19] | | X | | X | |
| Tumor Markers (AFP, βhCG)[20] | X | X | | | |
| Whole Blood Sample for PGx (optional)[21] | | X | | | |
| Post-progression Tumor Sample (optional)[22] | | | | X | |
| **Concomitant Medication** | X | X | | X | X |
| **AE[23]** | X | X | | X | X |

ADA: antidrug antibody; AE: adverse event; AFP: alpha-fetoprotein; βhCG: beta human chorionic gonadotropin; C: cycle; CT: computerized tomography; D: day; ECG: electrocardiogram; ECOG: European Cooperative Oncology Group; FFPE: formalin fixed paraffin embedded; ICF: informed consent form; INR: international normalized ratio; IRC: independent review committee; IRR: infusion-related reaction; IRT: interactive response technology; MRI: magnetic resonance imaging; PGx: pharmacogenomics; PT: prothrombin time; PTT: partial thromboplastin time; Q2W: every 2 weeks; RECIST: Response Evaluation Criteria In Solid Tumors; SAE: serious adverse event; T4: thyroxine; TSH: thyroid stimulating hormone

*Footnotes continued on next page*

*+5 day visit window does not apply to C1D1.

1. Screening: The Screening period is 45 days. Re-screening may be allowed upon discussion with the medical monitor. Central laboratory results should be used to confirm eligibility, however if repeat screening labs are required, local laboratory results can be used to confirm eligibility. The screening labs used to determine eligibility should be collected within 14 days prior to C1D1. In situations where laboratory results are outside of the permitted range, the investigator may opt to retest the subject and subsequent within range central lab screening results may be used to confirm eligibility. In case of multiple central laboratory data within the Screening period, the most recent data should be used to confirm eligibility. Subjects requiring transfusions to meet eligibility criteria are not eligible. Radiologic imaging used to confirm eligibility must be conducted within 28 days prior to C1D1.
2. All subjects will be treated for a maximum of 12 cycles or until the subject meets study treatment discontinuation criteria.
3. Study Treatment Discontinuation Visit (End of Study Treatment): The Study Treatment Discontinuation Visit will take place ≤ 7 days following the last dose or the decision by the investigator to discontinue study treatment.
4. 30-Day Safety Follow-up Visit: A 30-Day Safety Follow-up Visit should occur 30 days (+7 days) after the last dose of ASP1650 and will include the assessments as shown the in the Schedule of Assessments above.
5. Subject must have an available tumor specimen in a tissue block or-unstained serial slides, or subject is an appropriate candidate for tumor biopsy and is amenable to undergoing a tumor biopsy during the screening period. If a biopsy is performed, collection from a site other than lymph nodes is preferred. A minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 9 FFPE unstained slides are required. If ≥ 9 slides cannot be provided, the sponsor should be contacted for further guidance.
6. For subjects who signed an optional ICF, an optional on-treatment tumor specimen collected ± 7 days of the C4D1 visit may be provided. A minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 9 FFPE unstained slides are required. In cases where a pretreatment biopsy was performed, collection of the on-treatment specimen from the same site is preferred.
7. Confirmation of Inclusion/Exclusion Criteria must be completed on C1D1. Clinical safety lab results from the screening visit will be used to determine eligibility. If repeat screening labs are required, local laboratory results can be used to confirm eligibility.
8. Enrollment: After confirmation of eligibility, the pharmacist/designee will contact the IRT system in order to enroll the subject. Enrollment may be performed up to 3 days prior to C1D1.
9. ASP1650 will be administered as an intravenous infusion Q2W starting on C1D1. The 1000 mg/m$^2$ Q2W dose is administered as a 2-hour infusion and the 1250 mg/m$^2$ Q2W and 1500 mg/m$^2$ Q2W doses are administered as a 3-hour infusion. The infusion of ASP1650 should be completed in less than 6 hours from the start of infusion. Details of infusion preparation and storage requirements are defined in the pharmacy manual.
10. Post-infusion Observation Period: Following the first dose of ASP1650 on C1D1, the subject must be observed for 2 hours post ASP1650 infusion. If AEs are observed during this time, subsequent ASP1650 infusion times should be extended and subjects should continue to be observed for 2 hours post ASP1650 infusion. If the subject does not develop any AEs, the subject should be observed for 1-hour post-infusion for their subsequent ASP1650 infusions. The subject should be instructed to notify site personnel if they develop any AEs during this observation time period. In the event of grade 3 or 4 IRRs post ASP1650 infusion, samples for cytokine/chemokine should be collected. If any symptoms of potential anaphylaxis are observed, samples for tryptase should be collected.
11. Glucose Finger Prick: Due to the presence of the excipient trehalose (disaccharide) and dilution of ASP1650 with sterile 5% Dextrose Injection, a glucose check via finger prick at 1 hour post-infusion will be performed on Day 1 of all cycles. For diabetic subjects, additional glucose checks via finger prick should be performed as clinically indicated. If glucose check via finger prick is not available, glucose check via blood sampling is acceptable.

*Footnotes continued on next page*

12. Physical Exam: should include height (at Screening only), weight and ECOG performance status. All assessments should be taken predose on dosing days. A full physical exam is required at Screening. The physical exam only needs to be repeated on C1D1 if clinically significant changes from Screening are observed (in the opinion of the investigator). Targeted (symptom driven) physical exams should be conducted Q2W on day 1 of each cycle.
13. Vital signs (pulse, blood pressure, temperature) should be taken during every visit at the following time points:
    - Pre-dose at every visit
    - C1D1 and C2D1: Every 15 (± 5) minutes during ASP1650 infusion
    - Subsequent ASP1650 infusions: every 30 (± 10) minutes during ASP1650 infusions if the subject did not develop any AEs during the Post-infusion Observation Period of cycles 1 and 2. If subject develops AEs during C1D1, C2D1 or subsequent ASP1650 infusions, then collect every 15 (± 5) minutes during ASP1650 infusion
    - At 30 (± 10), 60 (± 10) and 120 (± 10) minutes post ASP1650 infusion during the Post-infusion Observation Period (for 1 or 2 hours; see footnote 10) 120 minute collection to be done only when observation period is 2 hours.
    - Unscheduled if clinically indicated
14. ECGs: a single ECG will be performed at Screening, the Study Treatment Discontinuation Visit, the 30-Day Follow-up Visit, and if clinically indicated or per local requirements. ECGs will be locally read. When collected on the same day, ECG should be collected prior to pharmacokinetic samples.
15. Imaging Assessments: Radiologic imaging will be evaluated at Screening (must be conducted within 28 days prior to C1D1) and every 6 weeks (+ 7 days) counting from C1D1 for the first 24 weeks and then every 12 weeks (± 7 days) thereafter until subject develops radiological disease progression per RECIST v1.1 by local investigator assessment or starts other systemic anticancer treatment, whichever comes earlier. Imaging will include CT scans with contrast of the thorax, abdomen, and pelvis. If CT scan with contrast is medically not feasible, MRI or CT scan without contrast may be used for imaging. Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease in bone or brain is suspected, respectively. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change.
16. Laboratory Assessments: Laboratory tests must be sent to the central laboratory for analysis. Central laboratory results should be used to confirm eligibility, however if repeat screening labs are required, local laboratory results can be used to confirm eligibility. Laboratory tests will be reviewed by the investigator prior to any study treatment. In the event that the central laboratory results are not available in time for treatment decisions, local certified laboratory tests may be used. Holidays and weekends should be taken into account when scheduling these collections. Additional assessments may be done centrally or locally to monitor AEs or as clinically indicated. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician.
17. Thyroid Function Tests (TSH and T4): Thyroid function tests will be collected at C1D1 predose, at the Study Treatment Discontinuation Visit, and during the study treatment period if clinically indicated.
18. Coagulation (PT, PTT and INR): Coagulation tests should be done at Screening, during study treatment period if clinically indicated and at Study Treatment Discontinuation Visit. Central lab results must be used to confirm eligibility. Ongoing evaluation should be continued for subjects who are receiving therapeutic anticoagulation according to local standard of care.

*Footnotes continued on next page*

19. Exploratory Biomarker (Serum and Plasma) samples should be taken at predose on day 1 of cycles 1, 2 and every other cycle (C4, C6 etc.) and at the Study Treatment Discontinuation Visit
    - C1D1: Predose
    - C2D1: Predose
    - C4D1: Predose
    - C6D1: Predose
    - C8D1: Predose
    - C10D1: Predose
    - C12D1: Predose
    - ASP1650 Study Treatment Discontinuation Visit
20. Tumor Markers (AFP and βhCG) Samples for the measurement of serum AFP and serum βhCG to be collected predose at every treatment cycle and during the post treatment period every 6 weeks + 7 days for the first 24 weeks and then every 12 weeks ± 7 days thereafter to align with imaging assessment until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment.
21. Optional PGx: for subjects who signed a separate ICF, an optional whole blood sample for PGx for exploratory biomarker analysis may be collected prior to first study drug administration.
22. Optional Post-Progression Tumor Sample: for subjects who signed a separate ICF, an optional post-progression tumor sample for exploratory biomarker analysis may be collected following disease progression per RECIST v1.1 by local investigator and prior to initiation of subsequent anticancer therapy.
23. AEs: AEs and SAEs (regardless of causality) will be collected from the time of signed informed consent through 30 days following the last dose of study treatment or until initiation of a new anticancer treatment, whichever comes first.

## Table 2 ASP1650 Pharmacokinetic and Immunogenicity Schedule

| Study Day (1 Cycle = 14 Days) | | Time (relative to dosing in each cycle) | Window | ASP1650 Pharmacokinetics Safety Lead-in Phase and all Subjects from Simon Stage I of Phase 2 | ASP1650 Pharmacokinetics Simon Stage II of Phase 2 | ASP1650 Immuno-genicity |
|---|---|---|---|---|---|---|
| Screening | | | | | | |
| Cycles 1 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | X |
| | | 1.5 hrs after start of infusion | ± 15 minutes | X | | |
| | | Immediately after end of infusion | within 10 minutes after the end of the infusion | X | X | |
| | | 0.5 hr after end of infusion | ± 5 minutes | X | | |
| | | 1.5 hrs after end of infusion | ± 15 minutes | X | | |
| | | 3 hrs after end of infusion | ± 15 minutes | X | | |
| | | 6 hrs after end of infusion | ± 30 minutes | X | | |
| | | 24 hrs after end of infusion | ± 120 minutes | X | | |
| | | 48 hrs after end of infusion | ± 120 minutes | X | | |
| | | 72 hrs after end of infusion | ± 120 minutes | X | | |
| Cycle 2 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | |
| Cycle 3 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | |
| | | 1.5 hrs after start of infusion | ± 15 minutes | X | | |
| | | Immediately after end of infusion | within 10 minutes after the end of the infusion | X | X | |
| | | 0.5 hr after end of infusion | ± 5 minutes | X | | |
| | | 1.5 hrs after end of infusion | ± 15 minutes | X | | |
| | | 3 hrs after end of infusion | ± 15 minutes | X | | |
| | | 6 hrs after end of infusion | ± 30 minutes | X | | |
| | | 24 hrs after end of infusion | ± 120 minutes | X | | |
| | | 48 hrs after end of infusion | ± 120 minutes | X | | |
| | | 72 hrs after end of infusion | ± 120 minutes | X | | |
| Cycle 4 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | |
| Cycle 5 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | X |
| Cycles 6 to 8 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | |
| Cycle 9 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | X |
| Cycles 10 to 12 | Day 1 | Predose (0 hr) | within 60 minutes prior to dosing | X | X | |
| Study Treatment Discontinuation Visit | | | | X | | X |
| 30-day Safety Follow-up Visit | | | | X | | X |

# 1 INTRODUCTION

Germ-cell tumors (GCTs) in male subjects are cancerous tumors derived from germ cells normally occurring inside the testicles and represent the most common solid tumor type in men between age 15 and 35 years [Einhorn, 1997]. An estimated 9,310 new cases of testicular germ cell cancer [Surveillance, Epidemiology, and End Results, 2017] will be diagnosed in the United States in 2018, including an estimated 4910 cases of pure seminomas and 4400 cases of nonseminomas. Pure seminomas are more sensitive to radiation while nonseminomas tend to grow and spread more quickly. A testicular tumor that contains both pure seminoma and nonseminoma cells is treated as a nonseminoma [National Cancer Institute, 2018].

Germ-cell tumors are remarkably chemosensitive with up to 80% of subjects with metastatic disease achieving cure with cisplatin-based combination chemotherapy [Adra et al, 2018; Hanna, 2014].

Subjects with tumors that relapse or progress after initial chemotherapy may be cured with salvage therapy including salvage surgery, standard dose chemotherapy, or high-dose chemotherapy plus peripheral-blood stem-cell transplant (PBSCT) [Adra et al, 2018; Feldman et al, 2010; Einhorn et al, 2007; Kondagunta et al, 2005; Loehrer et al, 1998; Murphy et al, 1993; Loehrer et al, 1986]. Despite these positive results with cisplatin-based front-line and salvage chemotherapy regimens and high dose chemotherapy with PBSCT, approximately 15% of GCT subjects are currently incurable and represent a subset of subjects with poor prognosis that are likely incurable with current available therapeutic options [Hartmann et al, 2001, Pont et al, 1997; Saxman et al, 1994]. Recently, a phase 2 trial of the immune checkpoint inhibitor pembrolizumab did not show any clinically meaningful single-agent activity (no partial or complete responses [CR]) in subjects with platinum refractory germ-cell tumors [Adra et al, 2018]. Therefore, a significant unmet medical need exists for these male subjects with incurable platinum refractory germ cell tumors. ASP1650 (IMAB027) is being developed with the goal of addressing this unmet medical need.

## 1.1 Background

ASP1650 is a novel chimeric mouse/human IgG1 antibody directed against the tumor-specific protein CLDN6, a primitive tight junction protein. The target is a member of the claudin family of more than 20 structurally related proteins that are involved in the formation of tight junctions in epithelia and endothelia [Niimi et al, 2001]. Tight junctions, together with adherens junctions and desmosomes, form the apical junctional complex in epithelial and endothelial cellular sheets. Adherens junctions and desmosomes are responsible for the mechanical adhesion between adjacent cells, whereas tight junctions are essential for the tight sealing of the cellular sheets forming a luminary barrier and controlling the paracellular ion flux.

CLDN6 expression is restricted to the embryo-fetal stage in humans and is virtually absent from any normal adult human tissue. However, it is frequently aberrantly expressed in various cancers of high medical need, including 93% of testicular, 56% of ovarian, and 23%

of uterine cancer tissue samples. In testicular cancer tissue samples, CLDN6 was expressed in 93% of seminomas and 95% of nonseminomas with > 65% of cases having > 80% of tumor cells expressing CLDN6. In ovarian cancer, CLDN6 expression is more frequent in prognostically worse settings (expression in higher International Federation of Gynecology and Obstetrics stage, metastatic lesions, less differentiated high-grade cancer cells).

This study is evaluating this first-in-class investigational drug, ASP1650, as a potential treatment for male subjects with incurable platinum refractory germ cell tumors.

## 1.2 Nonclinical and Clinical Data

### 1.2.1 Nonclinical Data

ASP1650 induced antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in testicular cancer cell lines expressing human CLDN6. ASP1650-directed cell killing was strictly dependent on the presence of CLDN6 and did not act via non-specific immune activation. In in vivo assessments, ASP1650 significantly inhibited testicular tumor growth in an immunocompromised xenografted mouse model. A combination of ASP1650 with platinum derivatives demonstrated a more potent antitumor effect than ASP1650 or chemotherapy alone.

CLDN6 is a cancer-specific antigen not expressed in normal adult human tissues and therefore, there is no specific target organ for testing of on-target toxicity. Cynomolgus monkeys were chosen as a non-rodent species to assess the effects of ASP1650 due to a CLDN6 tissue distribution and CLDN6 molecular sequence that was similar to humans. Also, the binding affinity of ASP1650 to cynomolgus and human orthologs of CLDN6 is identical and ASP1650-induced immune effector functions (ADCC, CDC) are comparable between both species.

Limited toxicological endpoints were studied in mice as this species was considered less predictive for testing whether ASP1650 might affect human safety due to CLDN6 expression in mouse pancreas, thyroid, and placenta and lower overall sequence homology between mouse and human compared to homology between cynomolgus monkey and human. Furthermore, the binding affinity of ASP1650 to the mouse ortholog is 10-fold lower compared to human CLDN6 and ASP1650-induced immune effector functions (ADCC, CDC) differ between mice and humans.

Safety pharmacology and toxicity of ASP1650 were assessed in 1 single ascending dose study in cynomolgus monkeys (intravenous administration, up to 100 mg/kg), one 29-day repeated dose study in mice (weekly intravenous administration of ASP1650 at doses up to 400 mg/kg). No target organs of toxicity were identified in these studies.

Two tissue cross-reactivity studies were conducted using human tissues. The results showed that ASP1650 did not bind to any normal adult human tissues except for intercalated duct cells of the pancreas (in 1 of 3 donors) and blood platelets (in all 3 donors).

Please refer to the current Investigator's Brochure (IB) for most recent nonclinical data.

### 1.2.2 Clinical Data

#### 1.2.2.1 Named Subject Use

Five subjects have received ASP1650 in the context of a named subject program setting for terminally ill subjects. ASP1650 treatment was rapidly escalated to high doses (920 mg/m$^2$ or 1000 mg/m$^2$), administered initially in weekly cycles and later in biweekly cycles over several months. These subjects included 2 subjects with ovarian cancer (the subjects received 52 and 13 treatment cycles, respectively), 1 subject with yolk sac tumor (10 treatment cycles), 1 subject with testicular cancer (64 treatment cycles) and 1 subject with uterine cancer (30 treatment cycles and still receiving treatment). ASP1650 was well tolerated in these subjects with no treatment-emergent adverse events (TEAEs) classified as related to ASP1650 reported by the treating physicians.

#### 1.2.2.2 Phase 1 Study 1650-CL-0101

Forty-two subjects were enrolled in a first-in-human (FIH), dose-escalation and dose-finding phase 1 study of ASP1650 in subjects with recurrent advanced ovarian cancer 1650-CL-0101 (EudraCT number: 2013-002755-15) referred to as OVAR. The primary study objectives were to determine the maximum tolerated dose (MTD) and to assess the safety and tolerability of ASP1650 with evaluation of antitumor activity as a secondary objective. Subjects meeting eligibility criteria were enrolled into 4 cohorts and received treatment with the following dosage levels: 1 to 100 mg/m$^2$, 300 mg/m$^2$, 600 mg/m$^2$ and 1000 mg/m$^2$.

There was limited evidence of antitumor activity with an objective response rate (ORR) of 2.4% (1/41 subjects with partial response [PR], no CR). However, median progression free survival (PFS) increased with increasing dose of ASP1650; the 95% CI for this parameter overlapped for the lowest and highest dose groups. Median overall survival (OS) ranged from 4.1 months in the 100 mg/m$^2$ cohort to 11.7 months in the stage 1/2 cohort (consisting of 1 patient treated up to 100 mg/m$^2$ and 1 patient treated with 300 mg/m$^2$).

Please refer to the current IB for most recent clinical data.

## 1.3 Summary of Key Safety Information for Study Drugs

The safety of ASP1650 for use in human clinical studies is supported by the virtual lack of expression of CLDN6 in normal adult tissues, the specificity of ASP1650 for its epitope, and that high doses, corresponding to 1200 mg/m$^2$ in humans, were well tolerated by cynomolgus monkeys. Based on tissue cross-reactivity studies, effects on pancreas and platelets are potential risks.

ASP1650 was well tolerated in 5 subjects that received ASP1650 in a named subject program setting for terminally ill subjects with no TEAEs classified as related to ASP1650 reported by the treating physicians.

As described above, 42 subjects were enrolled in a FIH, dose-escalation and dose-finding phase 1 study of ASP1650 in subjects with recurrent advanced ovarian cancer (EudraCT number: 2013-002755-15). The most commonly reported TEAEs in the study were fatigue, nausea, diarrhea and constipation. The majority of subjects in the study died due to

progressive disease (PD). Seven subjects permanently discontinued study drug due to the following TEAEs: intestinal obstruction, small intestinal obstruction, general physical health deterioration (2 subjects), intestinal perforation, ileus and gastroesophageal reflux disease. In general, safety assessments of laboratory evaluations, vital signs and electrocardiograms (ECGs) were clinically unremarkable. One grade 3 event of increased gamma glutamyltransferase did not resolve and was classified as a DLT with no MTD was identified in doses up to 1000 mg/m$^2$.

In this ongoing study (1650-CL-0201), as of 11 June 2019, 3 subjects have received a total of 8 doses of ASP1650 1000 mg/m$^2$ every 2 weeks and no DLTs have been reported.

Based on the available nonclinical and clinical data, potential risks of ASP1650 treatment are hypersensitivity, including infusion-related reactions (IRRs), and off-target activity on pancreatic tissue and platelets.

IRRs are a type of potential toxicity observed with infusion of monoclonal antibodies, The ability to define the clinical risk of cytokine release from the nonclinical data is limited, and CRS should be considered a potential risk for any monoclonal antibody (mAb) [Finco et al, 2014; Bugelski et al, 2009]. IRRs to monoclonal antibodies typically occur within 30 minutes to 2 hours after the start of drug infusion, but symptoms can be delayed for up to 24 hours. Most IRRs occur after the first or second exposure to the drug but up to 30% occur during subsequent treatments [LaCasce et al, 2018].

Details regarding potential risks are described in Section 5.2 of the IB. There are no expected adverse drug reactions for ASP1650 and the reference safety information (RSI) used for expedited health authority reporting is described in Section 5.2.3 of the IB.

## 1.4 Risk Benefit Assessment

ASP1650 is a novel chimeric mouse/human IgG1 antibody directed against the tumor-specific protein CLDN6, a primitive tight junction protein. CLDN6 is frequently expressed in testicular cancer tissue samples including 93% of seminomas and 95% of nonseminomas. ASP1650 induced ADCC and CDC in testicular cancer cell lines expressing human CLDN6. This study is evaluating this first-in-class investigational drug, ASP1650, as a potential treatment for male subjects with incurable platinum refractory germ cell tumors.

With respect to efficacy, ASP1650 significantly inhibited tumor growth and prolonged survival in a mouse testicular cancer xenograft model. Animals treated with 17.5 mg/kg (90.77%) or 35 mg/kg 3xW showed > 90% tumor growth inhibition (90.88%) with prolonged survival and had estimated ASP1650 trough concentrations of 50 and 100 µg/ml, respectively. Human pharmacokinetic data modeling and simulation based on results from the 1650-CL-0101 study support a dosing schedule of 1500 mg/m$^2$ once every 2 weeks (Q2W) that is anticipated to lead to a mean trough concentration of 144 µg/mL with approximately 80 and 60% of subjects having trough values above 50 and 100 µg/mL, respectively.

Based on currently available clinical data, ASP1650 was well-tolerated and most observed AEs have been manageable. Potential risks of ASP1650 are hypersensitivity, including IRRs, and effects on pancreatic tissue and platelets. Subjects receiving ASP1650 who experience an IRR during or after infusion may be premedicated prior to their next infusion and closely monitored for prevention of HSRs and IRRs. The other potential risks associated with ASP1650 can be managed by monitoring amylase, lipase, and platelet levels.

Based on the available clinical data, ASP1650 was well tolerated and no MTD was identified in doses up to 1000 mg/m$^2$. Although there was limited evidence of antitumor activity in the phase 1 study of ASP1650 in subjects with recurrent advanced ovarian cancer, clinical data from named subject use program suggest that ASP1650 may be beneficial in subjects with very advanced disease who have already received standard of care as well as experimental therapies. Overall, the potential benefits of ASP1650 outweigh the potential risks in subjects with CLDN6-positive cancers and the available data support this investigational study of male subjects with incurable platinum refractory germ cell tumors.

# 2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

## 2.1 Study Objective(s)

### 2.1.1 Primary Objective

- To establish the recommended phase 2 dose (RP2D) of ASP1650 in subjects with incurable platinum refractory germ cell tumors (Safety Lead-in Phase)
- To evaluate the efficacy of ASP1650 as measured by confirmed ORR, as assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (RECIST v1.1 and serum tumor biomarker [beta human chorionic gonadotropin [βhCG] and alpha-fetoprotein [AFP] response criteria), in subjects with incurable platinum refractory germ cell tumors (phase 2)

### 2.1.2 Secondary Objectives

- To evaluate the following efficacy measures:
  - Confirmed ORR by RECIST v1.1
  - Clinical benefit rate (CBR), as assessed by modified RECIST v1.1 and RECIST v1.1
  - Duration of response, as assessed by modified RECIST v1.1 and RECIST v1.1
  - PFS, as assessed by modified RECIST v1.1 and RECIST v1.1
- To evaluate safety and tolerability of ASP1650
- To evaluate the effect of ASP1650 on changes in serum βhCG and AFP
- To evaluate the pharmacokinetics of ASP1650

### 2.1.3 Exploratory Objectives

- To evaluate the immunogenicity profile of ASP1650
- To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome to ASP1650

## 2.2 Study Design and Dose Rationale

### 2.2.1 Study Design

This is a phase 2, open-label, single-arm, multicenter study to assess the safety and efficacy of ASP1650, an mAb targeting CLDN6, in male subjects with incurable platinum refractory germ cell tumors. Up to 46 subjects at approximately 4 centers located in the United States will participate in the study.

The study consists of 2 phases: Safety Lead-in phase and phase 2. For all subjects, the study will consist of the following periods: Screening, Enrollment, Treatment and Follow-up. Each subject may complete a maximum of 12 treatment cycles. One treatment cycle is 14 days. After discontinuation of study drug treatment, all subjects will complete a study treatment discontinuation visit and a safety Follow-up visit.

**Screening and Enrollment Period**

Screening will take place up to 45 days prior to enrollment. Re-screening may be allowed 1 time per subject upon discussion with the medical monitor.

**Treatment Period**

*Safety Lead-in Phase*

The Safety Lead-in phase of this study is to establish the tolerability of RP2D (ASP1650 1500 mg/m$^2$ [Q2W]). An initial dose level of ASP1650 1000 mg/m$^2$ Q2W will be evaluated in a 3-subject cohort (cohort 1), and if well tolerated, a new subject cohort (minimum 3 and up to 4 subjects) will be opened to evaluate a dose level of ASP1650 1500 mg/m$^2$ Q2W (cohort 2) according to the Bayesian Optimal Interval (BOIN) Design [Liu et al, 2015]. Based on tolerability observed in cohort 2, an additional subject cohort (cohort 3) will be opened to evaluate 1500 mg/m$^2$ Q2W (minimum 3 and up to 4 subjects) or de-escalation to 1250 mg/m$^2$ Q2W if 1500 mg/m$^2$ Q2W is not tolerable (minimum 6 and up to 8 subjects). Nine to 18 subjects will be enrolled in the Safety Lead-in phase. The RP2D determination will be based on at least 6 evaluable subjects at the RP2D as determined by the Dose Evaluation Committee (DEC).

There will be at least 3 calendar days between the treatment initiation of the first subject and treatment initiation of all subsequent subjects at the same dose level.

The dose limiting toxicity (DLT) observation period will be from cycle 1/day 1 (C1D1) through C2D14. Evaluable subjects are defined as subjects who experience a DLT or in the absence of DLT, complete the DLT observation period. Subjects who are later discovered not to meet eligibility criteria or are not evaluable for DLT may be replaced. If no DLTs are observed in the first 6 evaluable subjects (cohorts 1 and 2), the DLT observation period for cohort 3 may be reduced to C1D1 through C1D14 (one cycle).

Dose evaluation rules based on the BOIN design with target DLT rate of 0.30 and optimal interval of (0.236, 0.359) are as follows:

| | **Number of Subjects Treated at Current Dose Level** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Action** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Escalate dose if number of subjects with DLT ≤ | 0 | 0 | 1 | 1 | 1 | 1 | 2 |
| Stay at current dose level if number of subjects with DLT = | 1 | 1 | - | 2 | 2 | 2 | 3 |
| De-escalate if number of subjects with DLT = | 2* | 2 | 2 or 3 | 3 | 3 or 4 | 3 or 4 | 4 |
| Stop if number of subjects with DLT ≥ | 3 | 3 | 4 | 4 | 5 | 5 | 5 |

DLT: dose limiting toxicity.

*The study may be terminated instead of de-escalated upon discussion with the DEC.

The DEC will be responsible for the review of individual subject safety data in order to provide an assessment of whether reduction or escalation should occur within the next cohort and/or to determine when MTD has been reached in a given dose level. Additional details regarding responsibilities and membership requirements will be included in the DEC Charter.

**Proposed Dose Levels of ASP1650**

| **Dose Level** | **ASP1650** | **Planned Number of Subjects** |
|---|---|---|
| 1 | 1000 mg/m$^2$ | 3 |
| 2 | 1500 mg/m$^2$ | 6-8 |
| De-escalated | 1250 mg/m$^2$ | Only if necessary based on DLTs of Dose Level 2 |

DLT: dose limiting toxicity

At minimum, safety data from the DLT observation period are needed for the DEC meeting, however, all available safety findings, including those occurring after the designated DLT observation period that meet DLT criteria (“delayed DLT”), will be considered.

Subjects who are tolerating study drug at a dose level concurrently under review due to DLTs in another subject, are allowed to continue dosing through week 24, as unless otherwise directed by the DEC.

Enrollment of 3 subjects at the target RP2D (1500 mg/m$^2$ Q2W) will begin once the 1000 mg/m$^2$ Q2W dose level has been deemed tolerable. A de-escalation dose cohort will be opened at 1250 mg/m$^2$ Q2W if 1500 mg/m$^2$ Q2W has been deemed not tolerable. Subjects enrolled in the 1000 mg/m$^2$ Q2W dose level will continue treatment at that dose level (unless they meet study treatment discontinuation criteria) and will be dose escalated to the RP2D after the RP2D is deemed tolerable.

*Dose Limiting Toxicity Criteria*

A DLT is defined as any of the following adverse events (AEs; graded using National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] version 5.0) or laboratory findings that the investigator (or sponsor) cannot clearly attribute to a cause other than study drug:

- Grade 4 neutropenia or grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia; or grade 3 thrombocytopenia accompanied by bleeding that requires any transfusion
- Grade 4 anemia or grade 3 anemia requiring transfusion
- Grade ≥ 3 non-hematological AE
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN; grade ≥ 3) without liver metastases
- AST or ALT > 8 x ULN in subjects with liver metastases
- AST or ALT > 3 x ULN and total bilirubin > 2 x ULN (in subject with Gilbert syndrome: AST or ALT > 3 x ULN and **direct** bilirubin > 1.5 x ULN)
- Total bilirubin > 3 x ULN (grade ≥ 3)
- Amylase or lipase > 2 x ULN (grade ≥ 3)
- IRR that requires the infusion to be permanently discontinued

**Phase 2**

Once RP2D has been established as tolerable, up to 34 subjects will be enrolled in phase 2 to receive ASP1650 Q2W starting on C1D1 for up to a maximum of 12 cycles or until a study discontinuation criteria has been met, whichever occurs earlier. A Simon's 2-stage design is implemented to allow for early termination. In Simon Stage I (stage I), a total of 13 subjects, including subjects from the RP2D cohort of the Safety-Lead–in phase will be evaluated for response. If there is 1 or fewer responses among these 13 subjects, the study will be stopped early. Otherwise, an additional 21 subjects will be enrolled in Simon Stage II (stage II).

*Safety Lead-in and Phase 2 Assessments*

Radiologic disease assessment will be evaluated every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks ± 7 days thereafter until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment, whichever comes earlier. All measurable disease must be documented at Screening and re-assessed at each subsequent radiologic evaluation. Imaging will include CT scans with contrast of the thorax, abdomen and pelvis. If the CT scan with contrast is medically not feasible, a CT scan without contrast or magnetic resonance imaging (MRI) may be used for imaging. Bone scans (or focal X-ray) or brain imaging may be performed if metastatic disease is suspected. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change.

Blood will be drawn for the measurement of serum AFP and serum βhCG at day 1 of every cycle and during the post treatment period follow up period to align with imaging assessment (every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks

± 7 days thereafter) until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment.

Response assessments for the primary objective of this trial (ORR) will be made using modified RECIST v1.1. The same measurable and non-measurable lesions determined at baseline will be followed at subsequent timepoints according to RECIST v1.1. Response assessments by RECIST v1.1 and modified RECIST v1.1 will be based upon local investigator evaluation.

*Safety Assessments*

Safety assessments will include AEs, vital signs, ECGs, physical exams, Eastern Cooperative Oncology Group (ECOG) performance status and laboratory assessments. Severity of AEs and laboratory abnormalities will be assessed based on NCI-CTCAE.

*Biomarkers and Other Sampling*

An archival tumor specimen will be collected prior to first dose of study treatment. If archival tissue is unavailable or insufficient, a tumor biopsy may be performed during the screening period if the subject is an appropriate candidate for tumor biopsy.

Samples for pharmacokinetics, immunogenicity and biomarkers will be collected. An optional on treatment tumor tissue sample may be collected. Pharmacogenomics (PGx) and post-progression tumor samples may be collected for those subjects who sign separate informed consent forms (ICFs).

**Follow-up Period**

Following discontinuation from study treatment, subjects will have a Study Treatment Discontinuation Visit ≤ 7 days after their last dose of study drug or decision by the investigator to discontinue treatment, in addition to a Safety Follow-up visit at 30 days (+7 days) after their last dose of study drug.

If a subject discontinues study drug prior to radiologic progression, the subject should enter the Post-Treatment Follow-up Period. The subject should continue to undergo imaging assessments and serum AFP and serum βhCG every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks ± 7 days thereafter until 1 of the following events occurs:

- Radiological disease progression
- Subject starts another anticancer treatment

All post-progression anti-cancer therapies including date and site of progression will be recorded on the electronic case report form (eCRF).

### 2.2.2 Dose Rationale

The recommended target dose and schedule is 1500 mg/m$^2$, administered Q2W. This is based on consideration of both clinical and non-clinical efficacy and safety data.

With respect to efficacy, ASP1650 significantly inhibited tumor growth in a mouse testicular cancer xenograft model and prolonged survival over a dose of 4.375 mg/kg to 35 mg/kg three times a week (3xW) corresponding to estimated ASP1650 trough concentrations of 12.5 μg/mL to 100 μg/mL. Animals treated with 17.5 mg/kg (90.77%) or 35 mg/kg 3xW showed > 90% tumor growth inhibition (90.88%) with prolonged survival. The respective ASP1650 trough concentrations were estimated to be 50 and 100 μg/ml.

With respect to safety, no ASP1650-related toxicities were noted in either single dose study in cynomolgus monkeys or 28-day weekly intravenous dose study in mice (100 mg/kg). The MTD was not achieved in the 1650-CL-0101 study, as none of the AEs were considered dose limiting. Elevated amylase was reported in 3 subjects in the ovarian study, with 1 each in 100, 300 and 1000 mg/m$^2$ dose group. However, exposure safety analysis did not reveal any relationship between drug exposure and amylase values.

Using human pharmacokinetic data from the 1650-CL-0101 study, modeling and simulation results support a dosing schedule of 1500 mg/m$^2$ Q2W instead of the every 3 weeks (Q3W) schedule employed in the 1650-CL-0101 study. A dosing schedule of 1500 mg/m$^2$ Q2W is anticipated to lead to a mean trough concentration of 144 μg/mL with approximately 80 and 60% of subjects having trough values above 50 and 100 μg/mL, respectively.

A starting dose of 1000 mg/m$^2$ Q2W is recommended in this study, which represents a 30% higher dose intensity compared to 1000 mg/m$^2$ Q3W in the OVAR study. If no dose limiting toxicities are observed in 1000 mg/m$^2$ Q2W dose, the dose will be increased to 1500 mg/m$^2$ Q2W. This represents a 31% increase in $C_{max}$.

## 2.3 Endpoints

### 2.3.1 Primary Endpoints

- Establish RP2D of ASP1650 through DLT assessment by DEC.
- Confirmed ORR, defined as the proportion of subjects who have a best overall response of confirmed CR or confirmed PR, as assessed by modified RECIST v1.1

### 2.3.2 Secondary Endpoints

- Safety and tolerability, as measured by AEs, laboratory test results, vital signs, ECGs and ECOG performance status
- ORR by RECIST v1.1
- CBR, as assessed by modified RECIST v1.1 and RECIST v1.1
- Duration of response, as assessed by modified RECIST v1.1 and RECIST v1.1
- PFS, as assessed by modified RECIST v1.1 and RECIST v1.1
- Percent change in serum βhCG and AFP
- Pharmacokinetics of ASP1650 ($AUC_{336}$, $C_{max}$, $t_{max}$, $C_{trough}$)

### 2.3.3 Exploratory Endpoints

- Immunogenicity of ASP1650 as measured by the frequency of antidrug antibody positive subjects
- Potential genomic and/or other exploratory biomarkers that may be related to treatment outcome of ASP1650

# 3 STUDY POPULATION

## 3.1 Selection of Study Population

Male subjects with incurable platinum refractory germ cell tumors for whom no standard of care treatment exists or who are ineligible to receive available standard of care treatment based on investigator's clinical judgment will be selected for the study.

## 3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

*General Criteria:*

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization [HIPAA] for US sites) must be obtained from the subject or legally authorized representative (if applicable) prior to any study-related procedures.
2. Subject is male and considered an adult (e.g., ≥ 18 years of age in the US) according to local regulation at the time of signing the informed consent.
3. A male subject with female partner(s) of childbearing potential must agree to use contraception as detailed in Appendix 12.3 Contraception Requirements during the treatment period and for at least 6 months after the final study drug administration.
4. Subject must not donate sperm during the treatment period and for 6 months after the final study treatment administration.
5. A male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the study period and for 6 months after the final study treatment administration.
6. Subject agrees not to participate in another interventional study while receiving study drug in present study.

*Disease Specific Criteria:*

7. Subject has histological evidence of germ cell tumor. Subjects with seminoma and nonseminoma are eligible.
8. Subject must have a germ cell tumor that is not amenable to cure with either surgery or chemotherapy.

9. Subject must have received initial cisplatin based combination chemotherapy AND demonstrated progression following at least 1 salvage regimen for advanced germ cell neoplasm (including relapsed primary mediastinal nonseminomatous germ cell tumor).
    - Initial cisplatin based combination therapy includes bleomycin-etoposide-cisplatin, cisplatin-etoposide, etoposide-ifosfamide-cisplatin or similar regimens
    - "Salvage" regimens include high dose chemotherapy, paclitaxel-ifosfamide-cisplatin, vinblastine-ifosfamide-cisplatin or similar regimens
    - "Failure" of prior therapy is defined as:
        - A > 25% increase in the products of perpendicular diameters of measurable tumor masses during prior therapy, which are not amenable to surgical resection; OR
        - The presence of new tumor that are not amenable to surgical resection; OR
        - An increase in AFP or βhCG (≥ 50% increase in 2 separate samples collected at least 1 week apart are required if rising tumor markers are the only evidence of failure).

          NOTE: Subjects with clinically growing teratoma (enlarging mature teratoma arising during or after chemotherapy for a non-seminomatous germ-cell tumor and with normal serum levels of AFP and βhCG) should undergo surgical resection if feasible.
10. Subjects with late relapse (> 2 years) not amenable to resection are eligible.
11. Subjects must have evidence of recurrent or metastatic carcinoma by 1 or more of the following:
    - Subject has measurable disease according to RECIST v1.1 within 28 days prior to the first dose of study treatment. For subjects with only 1 measurable lesion and prior radiotherapy, the lesion must be outside the field of prior radiotherapy or must have documented progression following radiation therapy.
    - Subject has a baseline rising tumor marker (AFP or βhCG).

      NOTE: If a rising tumor marker is the only evidence of PD, at least 2 consecutive rising values at least 1 week apart are needed. Subjects with only evidence of disease as rising tumor marker AFP and βhCG will be assessed for alternate causes of increased serum levels of these markers, such as cross reaction with luteinizing hormone (LH) (can be tested if needed by testosterone suppression of LH), hepatitis, use of marijuana or second primary tumor.

*Physical or Laboratory Findings:*

12. Subject must have an available tumor specimen in a tissue block or unstained serial slides, or subject is an appropriate candidate for tumor biopsy as determined by the investigator and is amenable to undergoing a tumor biopsy during the screening period.
13. Subject has ECOG performance status of 0 to 2.

14. Subject must meet all of the following criteria based on the centrally analyzed laboratory tests within 14 days prior to the first dose of study treatment. If repeat screening labs are required, local laboratory results can be used to confirm eligibility. In case of multiple central laboratory data within this period, the most recent data should be used to determine eligibility.
    - Hemoglobin ≥ 8 g/dL
    - Absolute neutrophil count ≥ 1.0 x $10^9$/L
    - Platelets ≥ 75 x $10^9$/L
    - Albumin ≥ 2.5 g/dL
    - Total bilirubin ≤ 2 x ULN or direct bilirubin ≤ ULN for subjects with total bilirubin levels > 2 x ULN
    - AST and ALT ≤ 2.5 x ULN without liver metastases (or ≤ 5 x ULN if liver metastases are present)
    - Estimated glomerular filtration rate ≥ 30 mL/min/1.73 $m^2$
    - Prothrombin time/international normalized ratio and partial thromboplastin time (PTT) ≤ 2 x ULN (except for subjects receiving anticoagulation therapy)

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

## 3.3 Exclusion Criteria

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

*Prohibited Treatment or Therapies:*

1. Subject has received systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to first dose of study treatment. Subject using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone) or a single dose of systemic corticosteroids is eligible. Subject who received systemic steroids for asymptomatic CNS metastases within 14 days prior to first dose of study treatment is eligible.
2. Subject has received other investigational agents or devices within 28 days prior to first dose of study treatment.
3. Subject has had a prior anti-cancer mAb within 4 weeks prior to study day 1 or has not recovered (i.e., ≤ grade 1 or at baseline) from AE due to mAb agents administered more than 4 weeks earlier.
4. Subject has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or has not recovered (i.e., ≤ grade 2 or at baseline) from AEs due to a previously administered agent.

*Medical History or Concurrent Disease:*

5. Subject has prior severe allergic reaction or intolerance to an mAb, including humanized or chimeric antibodies that required permanent discontinuation.

6. Subject has known immediate or delayed hypersensitivity, intolerance or contraindication to any component of study treatment.
7. Subject has an active human immunodeficiency virus (HIV) infection or known active hepatitis B (HBsAg) or C infection. Subjects with well-controlled HIV infections (i.e., without detectable viral load) are eligible. For subjects who are negative for HBsAg, but HBcAb positive, an HBsAg DNA test will be performed and if positive, the subject will be excluded. Subjects with positive serology but negative hepatitis C virus (HCV) RNA test results are eligible.
8. This criterion has been removed.
9. Subject has active infection requiring systemic therapy that has not completely resolved within 14 days prior to first dose of study treatment.
10. Subject has symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Subject with asymptomatic CNS metastases is eligible.
11. Subject has had a major surgical procedure and has not completely recovered within 28 days prior to the first dose of study treatment.
12. Subject has psychiatric illness or social situations that would preclude study compliance, per investigator's judgment.
13. Subject has another malignancy for which treatment is required per investigator's clinical judgment. Subject with negligible risk of metastasis or death per investigator's clinical judgment is eligible (e.g., basal or squamous cell skin cancer, localized prostate cancer treated with curative intent or incidental prostate cancer T1-T2a, Gleeson $\leq 3 + 4$, PSA $\leq 0.5$ and who are undergoing active surveillance).
14. Subject has any concurrent disease, infection, or co-morbid condition that interferes with the ability of the subject to participate in the study, which places the subject at undue risk or complicates the interpretation of data in the opinion of the investigator.

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

# 4 TREATMENT(S)

## 4.1 Identification of Investigational Product(s)

### 4.1.1 Study Drug(s)

ASP1650 will be supplied by Astellas as a sterile lyophilized powder preparation with the chimeric mAb ASP1650 as the active pharmaceutical ingredient.

Each vial contains 200 mg ASP1650 and has to be reconstituted with 4.4 mL sterile water for injection to a concentration of 45 mg/mL. Further dilution with sterile 5% Dextrose Injection, USP to a final concentration of 2 to 25 mg/mL according to assigned dose level is required. All excipients are animal component free and of compendial grade (European Pharmacopoeia [Ph. Eur.], current version). No preservatives are contained, since the vial is designed for single use.

The investigational product should be stored at -20°C ± 5°C. Temperature should be controlled and monitored. Details of investigational product receipt, labeling, storage and preparation are provided in the Pharmacy Manual.

## 4.2 Packaging and Labeling

ASP1650 will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD-Astellas US Technologies, Inc. (AUST) or sponsor's designee in accordance with APGD-AUST or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

The container closure system consists of a clear glass vial DIN 20R (20 mL), Ph. Eur. Hydrolytic class I, a vacuum stopper consisting of the basic polymer bromobutyl and the filler silicate and a crimping cap (aluminum). The vials carry a blue colored flip off cap.

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

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

## 4.3 Study Drug Handling

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

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- Any unused study drug is returned to the sponsor.

Study drug inventory and accountability records will be kept by the investigator, head of study site or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator, head of study site or designee agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator, head of study site or designee (i.e., study drug manager) will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator, head of study site or designee (i.e., study drug manager). The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator, head of study site or designee (i.e., study drug manager) agrees to conduct a final drug supply inventory and

to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.

- The site staff must return study drug to the sponsor or designee at the end of the study or upon expiration unless otherwise approved by the sponsor.
- Study drugs provided by Astellas will not be destroyed on-site, unless considered hazardous materials or drugs for which the clinical unit SOP dictates destruction must be handled by the institution. Destruction must not occur until final study drug accountability reconciliation has been performed and sponsor has approved destruction in writing.

## 4.4 Blinding

This section is not applicable as this is an open-label study.

## 4.5 Assignment and Allocation

Subjects will be enrolled through Interactive Response Technology (IRT). The site personnel will dispense the treatment according to the IRT system's assignment. Specific procedures for enrollment through the IRT are contained in the study procedures manual.

# 5 TREATMENTS AND EVALUATION

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

### 5.1.1 Dose/Dose Regimen and Administration Period

Aseptic technique must be used for the preparation and administration of ASP1650. Detailed instructions for the administration of ASP1650 will be provided in the Pharmacy Manual.

ASP1650 will be administered intravenously on day 1 of each cycle (each cycle has 14 days). All subjects will be treated for a maximum of 12 cycles or until the subject meets study treatment discontinuation criteria.

The 1000 mg/m$^2$ Q2W dose is administered as a 2-hour infusion and the 1250 mg/m² Q2W and 1500 mg/m² Q2W doses are administered as a 3-hour infusion, any of which may be interrupted or slowed down to manage toxicity.

The infusion of ASP1650 should be completed in less than 6 hours from the start of infusion.

### 5.1.2 Increase or Reduction in Dose of the Study Drug(s)

#### 5.1.2.1 ASP1650 Increase or Reduction

Following the safety lead-in, subjects will be treated with the RP2D of ASP1650. Subjects enrolled in the 1000 mg/m$^2$ Q2W dose level in the Safety Lead-in phase will be dose escalated to 1500 mg/m$^2$ after the RP2D has been deemed tolerable. Dose increase above the RP2D is not allowed. If the tolerable RP2D is established as 1500 mg/m$^2$ Q2W, then dose

reduction to 1250 mg/m$^2$ Q2W is allowed due to AEs, per investigator discretion. Further dose reduction to 1000 mg/m$^2$ Q2W is allowed due to AEs, per investigator discretion, however, dose reduction below 1000 mg/m$^2$ Q2W is not allowed. Dose re-escalation is allowed up to the RP2D based on investigator discretion. Body surface area should only be recalculated if there is a weight change of at least 10% since the last body surface area calculation.

#### 5.1.2.2 ASP1650 Interruption or Permanent Discontinuation

There is a +5 day allowable window for dosing ASP1650 (with the exception of C1D1). If ASP1650 treatment is delayed more than 2 days then it should be administered as soon as the reason for delay has resolved, which will then become day 1 of the next cycle. Permanently discontinue ASP1650 treatment if delayed beyond 28 days from when the next study treatment was scheduled to be administered. However, restarting study treatment after dosing delay (beyond ≥ 28 days from when the next study treatment was scheduled to be administered) may be allowed based on investigator consultation with, and approval of, the Astellas medical monitor.

#### 5.1.2.3 Guidelines for Infusion-Related Reactions for ASP1650

Subjects should be closely monitored for IRRs during infusion and post-infusion to facilitate early identification and management. The management of such toxicities should be based on investigator utilizing institutional standard of care, published guidelines and the general guidelines provided in Table 3 below.

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

Not all anaphylactic reactions manifest as anaphylactic shock. Because anaphylaxis can recur and worsen with re-exposure, permanently discontinue ASP1650 for any subject having a reaction with features (even if mild) that are highly suggestive of anaphylaxis.

**Table 3 Infusion-Related Reactions**

| **Infusion-Related Reactions** | |
|---|---|
| **CTCAE Grade** | **Management** |
| Grade 1 standard infusion reaction | Continue infusion and closely monitor the subject.<br>For the next infusion:<br>• Pre-medicate as appropriate.*<br>• Closely monitor the subject for symptoms and signs of an infusion reaction. |
| Grade 2 standard infusion reaction | Interrupt.<br>Medical management as per type of reaction. Resume infusion once toxicity Grade ≤ 1 and reduce the infusion rate for the remaining infusion.<br>For the next infusion:<br>• Increase total infusion time (reduce infusion rate).<br>• Pre-medicate as appropriate.*<br>• Closely monitor the subject for symptoms and signs of an infusion reaction. |
| Grade 3 or 4 standard infusion reactions or any reaction with features of anaphylaxis | Stop the infusion immediately.<br>Institute appropriate medical management immediately based on the type of reaction.<br>Permanently discontinue ASP1650<br>Once the subject has been stabilized, collect blood for a cytokine/chemokine panel.<br>If the reaction is suggestive of anaphylaxis, collect blood for serum total tryptase level (levels typically peak within 3 hours after the onset of symptoms). |

CTCAE: Common Toxicity Criteria for Adverse Events

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

### 5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

Previous treatment is defined as medication and non-medication therapy (e.g., diet, sodium intake restriction, rehabilitation, etc.) undergone before entering the investigational period.

*Prohibited Prior Treatment or Therapies*

- Systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to first dose of study treatment. Subject using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone) or a single dose of systemic corticosteroids is eligible. Subject who received systemic steroids for asymptomatic CNS metastases within 14 days prior to first dose of study treatment is eligible.
- Other investigational agents or devices within 28 days prior to first dose of study treatment.

- Prior anti-cancer mAb within 4 weeks prior to study day 1 or ongoing toxicity (i.e., > grade 1 or at baseline) from AE due to mAb agents administered more than 4 weeks earlier.
- Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or ongoing toxicity (i.e., > grade 2 or at baseline) from AEs due to a previously administered agent

Concomitant treatment means medication and non-medication therapy (e.g., opioids, sodium intake restriction, rehabilitation, etc.) used during the investigational period.

All concomitant treatments will be recorded in the eCRF.

*Prohibited Concomitant Treatment*

The following are strictly prohibited:

- Systemic immunosuppressive agents:
    - Concurrent systemic immunosuppressive therapy, in particular systemic corticosteroids, must be stopped 14 days prior to first dose of study treatment. However, subjects are allowed to initiate use of systemic steroids for CNS metastases after the first dose of study treatment.
    - Subjects are allowed to use a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone or up to 10 mg per day of prednisone) or a single dose of systemic corticosteroids.
- Other systemic chemotherapy, immunotherapy, radiotherapy, herbal medications or other treatments intended for antitumor activity. Palliative radiotherapy for peripheral bone metastases is allowed.
- Investigational products or therapy other than ASP1650.

*Cautionary Concomitant Treatment*

Considerations should be given to avoid or minimize the use of the following concomitant medications, if possible, during ASP1650 treatment:

- Systemic corticosteroids, because their impact on the potential efficacy of ASP1650 is not known.
    - Systemic corticosteroids should be avoided or minimized while subject is on study treatment unless required for management of an emergent medical condition (e.g., severe hypersensitivity reaction).
    - For a subject's first dose of ASP1650, it is recommended that the prophylactic use of corticosteroids be avoided.
    - Inhaled, intranasal and topically applied steroids are allowed.

*Prohibited Non-drug Procedures*

- Any surgery (including palliative) that involves removal of tumor/metastases masses that may affect the efficacy assessments (removal of small non-measurable masses may be allowed)

A list of excluded medications can be found in [Appendix 12.1 List of Excluded Concomitant Medications].

### 5.1.4 Treatment Compliance

The dose and schedule of ASP1650 administered to each subject will be recorded on the appropriate form at every cycle. Reasons for dose delay, reduction or omission will also be recorded. This information will be used to assess compliance with the treatment.

Compliance with infusion administration and dosing should be monitored closely and any deviations should be reported to the sponsor.

### 5.1.5 Criteria for Continuation of Treatment

Subjects will be treated with ASP1650 on day 1 of each cycle (each cycle has 14 days). All subjects will be treated for a maximum of 12 cycles or until the subject meets study treatment discontinuation criteria. ASP1650 will not be made available after conclusion of the study to subjects who are still receiving and benefiting from study treatment.

In case of premature study termination, ASP1650 may be made available to subjects who are still receiving study treatment, have not yet completed 12 cycles of treatment and who are still benefiting from study treatment until study defined treatment discontinuation criteria is met.

## 5.2 Demographics and Baseline Characteristics

### 5.2.1 Demographics

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

### 5.2.2 Medical History

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

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

A complete medical history of the target disease will be recorded at screening. This will include:

- Subject's medical condition
- Date of initial diagnosis
- Tumor location
- Other disease specific information as designated in the eCRF.

## 5.3 Efficacy and Immunogenicity Assessments

### 5.3.1 Efficacy Assessments

Disease response and progression will be evaluated in this study using modified RECIST v1.1, incorporating RECIST v1.1 and serum tumor biomarker response criteria. In addition, response assessment using RECIST v1.1 alone for subjects with measurable disease at baseline and serum tumor biomarker response criteria alone for subjects with elevated serum tumor markers (> 2 x ULN AFP or > 2 x ULN βhCG) at baseline will be performed as sensitivity analyses.

#### 5.3.1.1 Imaging Assessments

Imaging assessments will be evaluated by the investigator at baseline and every 6 weeks + 7 days counting from C1D1 during the first 24 weeks and then every 12 weeks ±7 days thereafter until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment, whichever comes earlier.

All measurable disease must be documented at Screening and re-assessed at each subsequent radiologic evaluation. Imaging will include CT scans with contrast of the thorax, abdomen and pelvis. If the CT scan with contrast is medically not feasible, a CT scan without contrast or MRI may be used for imaging. Bone scans (or focal X-ray) may be performed if metastatic disease in bone is suspected. The same mode of imaging should be utilized throughout the study unless medical necessity requires a change.

Assessment of response using RECIST v1.1 [Eisenhauer et al, 2009] will be based upon local investigator evaluation. Confirmatory scans for CR or PR should be done at least 4 weeks after the date of the scan that CR or PR was first observed.

Response assessments for the primary objective of this trial (ORR) will be made using modified RECIST v1.1. The same measurable and non-measurable lesions determined at baseline will be followed by RECIST v1.1 throughout the study.

#### 5.3.1.2 Response Criteria Based on Modified RECIST v1.1

For subjects with measurable disease at baseline, the following criteria in Table 4 will be used:

**Table 4 Response Criteria Based on Modified RECIST v1.1**

| Serum Markers | Target Lesions | Non-Target Lesions | | New Lesions | Overall Timepoint Response Assessment |
|---|---|---|---|---|---|
| | (target lesion response) | (non-target lesion response) | | (unequivocal new lesions) | |
| Values that fall below the ULN for the assay employed | CR | CR | | No or Equivocal | CR |
| | CR | Not Applicable | | No or Equivocal | CR |
| | Not applicable | CR | | No or Equivocal | CR |
| For both AFP and beta-hCG, no increase ≥ 50% in 2 samples at least 1 week apart compared to nadir values, at least one of the values are above ULN | CR | CR | | No or Equivocal | PR |
| | CR | Not Applicable | | No or Equivocal | PR |
| | Not applicable | CR | | No or Equivocal | PR |
| For both AFP and beta-hCG, no increase ≥ 50% in 2 samples at least 1 week apart compared to nadir values | CR | Non-CR/Non-PD | | No or Equivocal | PR |
| | CR | NE/ND | | No or Equivocal | PR |
| | PR | CR | = not PD | No or Equivocal | PR |
| | PR | Non-CR/Non-PD | = not PD | No or Equivocal | PR |
| | PR | NE/ND | = not PD | No or Equivocal | PR |
| | PR | Not applicable | = not PD | No or Equivocal | PR |
| For both AFP and beta-hCG, no increase ≥ 50% in 2 samples at least 1 week apart compared to nadir values | SD | CR | = not PD | No or Equivocal | SD |
| | SD | Non-CR/Non-PD | = not PD | No or Equivocal | SD |
| | SD | NE/ND | = not PD | No or Equivocal | SD |
| | SD | Not applicable | = not PD | No or Equivocal | SD |
| Any | PD | Any | | Any | PD |
| Any | Any | PD | | Any | PD |
| Any | Any | Any | | Yes or Unequivocal | PD |
| Increase ≥ 50% in serum tumor markers AFP or beta-hCG in 2 samples at least 1 week apart compared to nadir values | Any | Any | | Any | PD |
| NE/ND | NE/ND | Not PD | | No or Equivocal | NE |

CR: complete response; ND: not done; NE: non-evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

Confirmatory assessment for CR or PR should be done at least 4 weeks after the date of the CR or PR was first observed.

In subjects whose only evidence of disease is elevated serum tumor markers (> 2 x ULN AFP or > 2 x ULN βhCG) at baseline, the modified RECIST v1.1 will reduce to serum tumor marker response criteria described in Section 5.3.1.3. In subjects whose only evidence of disease is elevated serum tumor markers (> 2 x ULN AFP or > 2 x ULN βhCG) at baseline, confirmatory assessment for CR or PR is not required.

#### 5.3.1.3 Response Criteria Based on Serum Tumor Biomarkers

Blood will be drawn for the measurement of serum AFP and serum βhCG at day 1 of every cycle and during the post treatment period follow up period to align with imaging assessment (every 6 weeks + 7 days counting from C1D1 for the first 24 weeks and then every 12 weeks ± 7 days thereafter) until the subject develops radiological disease progression per RECIST v1.1 by local investigator evaluation or starts other systemic anticancer treatment. To evaluate the effect of ASP1650 on changes in serum βhCG and AFP, disease response will be derived for subjects with elevated serum tumor markers (> 2 x ULN AFP or > 2 x ULN βhCG) at baseline using the following definition:

- CR is defined as values that fall below the ULN for the assay employed. Confirmed CR must remain at that level for at least 4 weeks.
- PR is defined by serum tumor markers (AFP and βhCG) that are decreasing. Elevated serum tumor markers (AFP or βhCG) values must fall ≥ 90% below baseline pretreatment levels for βhCG or 50% decrease below baseline pretreatment levels for AFP. PR must persist for at least 6 weeks to be a confirmed PR. If both tumor markers are elevated and 1 falls below 90%, the other should fall at least below 50% of baseline pretreatment levels.
- Stable disease (SD) is defined as no change or a change in serum tumor biomarkers that does not qualify as CR, PR or PD. Durable SD is defined as SD that is maintained for at least 12 weeks.
- PD is defined as ≥ 50% increase in AFP or βhCG in 2 samples, 1 week apart compared to nadir.

### 5.3.2 Immunogenicity Assessments

Serum samples to assess the formation of anti-drug antibodies against ASP1650 will be collected as outlined in the Schedule of Assessments [Table 1]. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a sponsor designated analytical laboratory using validated analytical methods. Refer to the Laboratory Manual for more detailed information.

## 5.4 Safety Assessment

### 5.4.1 Vital Signs, Height and Weight

Vital signs will include systolic and diastolic blood pressure (mmHg), radial pulse (beats/min) and temperature. All vital signs will be measured in a consistent manner (with the subject in the sitting or supine position) throughout study participation.

Height and weight will be measured using standard institution practice and equipment.

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

### 5.4.2 Observation Period Following ASP1650 Infusion

Following the first dose of ASP1650 on C1D1, the subject must be observed for 2 hours post ASP1650 infusion. If AEs are observed during this time, subsequent ASP1650 infusion times should be extended and subjects should continue to be observed for 2 hours post ASP1650 infusion. If the subject does not develop any AEs, the subject should be observed for 1 hour post-infusion for their subsequent ASP1650 infusions. The subject should be instructed to notify site personnel if they develop any AEs during this observation time period.

In the event of grade 3 or 4 IRRs, additional samples should be collected as follows:

- Once the subject has been stabilized, blood for cytokine/chemokine panel should be collected for shipment to central laboratory
- If any symptoms of potential anaphylaxis are observed, samples for tryptase should be collected for shipment to the central laboratory

In addition, due to the presence of the excipient trehalose (disaccharide) and dilution of ASP1650 with sterile 5% Dextrose Injection, a glucose check via finger prick at 1 hour post-infusion will be performed on Day 1 of all cycles. If a glucose check via finger prick is not available, glucose check via blood sampling is acceptable.

### 5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. See Schedule of Assessments [Table 1] for study visit collection dates. All laboratory tests must be sent to the central laboratory for analysis.

Central laboratory results should be used to confirm eligibility, however if repeat screening labs are required, local laboratory results can be used to confirm eligibility. The screening labs used to determine eligibility should be collected within 14 days prior to C1D1. In situations where laboratory results are outside of the permitted range, the investigator may

opt to retest the subject and subsequent within range screening central lab results may be used to confirm eligibility. In case of multiple central laboratory data within the Screening period, the most recent data should be used to confirm eligibility. Subjects requiring transfusions to meet eligibility criteria are not eligible.

Laboratory tests will be reviewed by the investigator prior to any study treatment. In the event that the central laboratory results are not available in time for treatment decisions, local certified laboratory tests may be used.

Holidays and weekends should be taken into account when scheduling these assessments.

Additional assessments may be done centrally or locally to monitor AEs or as clinically indicated. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician.

| **Panel/Assessment** | **Parameters to be Analyzed** |
|---|---|
| Hematology | Hematocrit (Hct)<br>Hemoglobin (Hgb)<br>Red Blood Cell Count (RBC)<br>White Blood Cell Count (WBC)<br>WBC differential<br>Absolute Neutrophil Count (ANC)<br>Platelets<br>Mean Corpuscular Volume (MCV)<br>Mean Corpuscular Hemoglobin (MCH)<br>Mean Corpuscular Hemoglobin Concentration (MCHC) |
| Biochemistry | Albumin<br>Blood Urea Nitrogen (BUN)<br>Calcium<br>Bicarbonate<br>Chloride<br>Creatinine<br>Estimated glomerular filtration rate<br>Glucose<br>Magnesium<br>Phosphate<br>Potassium<br>Sodium<br>Total Bilirubin<br>Total Protein<br>Alanine Aminotransferase (ALT)<br>Alkaline Phosphatase (ALP)<br>Aspartate Aminotransferase (AST)<br>Amylase<br>Lipase |
| *Table continued on next page* | |

| Panel/Assessment | Parameters to be Analyzed |
|---|---|
| Urinalysis | Color<br>Clarity/turbidity<br>pH<br>Specific gravity<br>Glucose<br>Ketones<br>Nitrites<br>Leukocyte esterase<br>Bilirubin<br>Urobilinogen<br>Blood<br>Protein<br>Microscopic urinalysis to be performed if abnormal dipstick |
| Grade 3 or 4 IRR | Cytokine/Chemokine Panel* |
| Any reaction with features of anaphylaxis | Serum Total Tryptase* |
| Biomarkers | Alpha-fetoprotein (AFP)<br>Beta human chorionic gonadotropin (βhCG) |
| Coagulation | Prothrombin time (PT) (sec)<br>Partial Thromboplastin Time (PTT)<br>International normalized ratio (INR) |
| Thyroid Function Test | Thyroid stimulating hormone (TSH)<br>Free T4 (thyroxine) |

*as applicable

### 5.4.4 Physical Examination

Physical examinations will be conducted at visits as outlined in the Schedule of Assessments [Table 1]. Each physical exam should include height (at Screening only), weight and ECOG performance status.

A full physical exam is required at Screening. The physical exam only needs to be repeated at C1D1 if clinically significant changes from the screening are observed (in the opinion of the investigator).

The ECOG scale will be used to assess performance status [see Appendix 12.8 ECOG Performance Status Scale].

### 5.4.5 Electrocardiogram

A single 12-lead ECG will be performed at the timepoints outlined in the Schedule of Assessments [Table 1]. Prior to performing ECG, subjects should rest in supine position for 10 minutes. When collected on the same day, ECG should be collected prior to pharmacokinetic samples. Additional ECG may be performed based on medical history and investigator medical judgment. ECGs will be read locally.

### 5.4.6 Order of Assessments

The following sequence order is recommended when more than 1 assessment is required at a time point with blood sampling for pharmacokinetics/metabolic profiling being collected nearest to the scheduled time point:

1. ECOG
2. ECG
3. Vital signs (blood pressure and heart rate)
4. Any type of blood draw as the last assessment.

NOTE: This order of events can be changed if required in order to accommodate pharmacokinetic time points and is not mandatory.

## 5.5 Adverse Events and Other Safety Aspects

### 5.5.1 Definition of Adverse Events

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

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent and will be collected until 30 days after the last dose of study drug or the subject is determined to be a screen failure.

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

#### 5.5.1.1 Abnormal Laboratory Findings

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

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

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

#### 5.5.1.2 Potential Cases of Drug-Induced Liver Injury

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

#### 5.5.1.3 Disease Progression and Study Endpoints

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

- Disease Progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. These data will be captured as efficacy assessment data as outlined in [Section 5.3 Efficacy and Immunogenicity Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE. All deaths up to 30 days after the last dose of study drug must be reported as an SAE, even if attributed to disease progression.
- Disease progression can be considered as the worsening of a subject's condition attributable to germ cell tumor. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastases to the primary cancer under study should be considered as disease progression not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study
- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

### 5.5.2 Definition of Serious Adverse Events (SAEs)

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

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

hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.)
- Other medically important events (defined in paragraph below)

Medical and scientific 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 subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### 5.5.2.1 Always Serious Adverse Events

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered by the sponsor to be an SAE per this classification as "always serious", additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested.

### 5.5.3 Criteria for Causal Relationship to Study Drug

A medically qualified investigator is obligated to assess the relationship between the study drug and each occurrence of each (S)AE. This medically qualified investigator will use medical judgment, as well as the RSI [Section 1.3 Summary of Key Safety Information for Study Drugs], to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

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

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

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

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.

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

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

### 5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-CTCAE guidelines (version 5.0). The items that are not stipulated in the NCI-CTCAE version 5.0 will be assessed according to the criteria below and entered into the eCRF.

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

### 5.5.5 Reporting of Serious Adverse Events (SAEs)

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue until 30 days*)* after the last dose of study drug or the subject is determined to be a screen failure.

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

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

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

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/special situations worksheet to:

Astellas Pharma Global Development – United States
Pharmacovigilance
Fax number: 888-396-3750
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and on the eCRF.

The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness criteria),
- Causal relationship to the study drug (including reason), and
- The drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., suspected unexpected serious adverse reaction (SUSAR) reporting) according to current local/regional regulatory requirements in participating countries. The sponsor or sponsor's designee will submit expedited safety reports (e.g.,

Investigational New Drug [IND] Safety Reports, SUSAR, Council for International Organizations of Medical Sciences-I [CIOMS-I] form) to Competent Authorities (CAs) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs that require submission per local requirements, IRB/local IEC/head of the study site.

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

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the safety, welfare, or rights of the subject.

### 5.5.6 Follow-up of Adverse Events

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

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

### 5.5.7 Monitoring of Common Serious Adverse Events

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

### 5.5.8 Adverse Events of Special Interest

IRRs are considered AEs of special interest. Subjects should be evaluated carefully for potential IRRs. In the event a subject is diagnosed with an IRR, then it should be reported as an AE. Additional information on the AE of IRR will be collected on the AE eCRF. If the

IRR is also classified as serious, they are to be collected via the SAE worksheet and reported within 24 hours.

### 5.5.9 Special Situations

Certain special situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug, comparator, or background therapy) are collected in the eCRF, as protocol deviation per [Section 8.3 Major Protocol Deviations] or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the SAE worksheet.

The special situations are:

- Pregnancy
- Medication error, overdose and “off-label use”
- Misuse/abuse
- Occupational exposure
- (Suspicion of) transmission of infectious agent
- Suspected drug-drug interaction

#### 5.5.9.1 Pregnancy

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing and report the information to sponsor according to the timelines in [Section 5.5.5 Reporting of Serious Adverse Event**s**] using the Pregnancy Reporting Form.

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

For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form.

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

- ″Spontaneous abortion″ includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.

- If an infant dies more than 1 month after the birth, the death is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

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

#### 5.5.9.2 Medication Error, Overdose and "Off-label Use"

If a medication error, overdose or "off- label use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 8.3 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

#### 5.5.9.3 Misuse/Abuse

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

#### 5.5.9.4 Occupational Exposure

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

#### 5.5.9.5 (Suspicion of) Transmission of Infectious Agent

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

#### 5.5.9.6 Suspected Drug-Drug Interaction

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

### 5.5.10 Supply of New Information Affecting the Conduct of the Study

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

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

### 5.5.11 Urgent Safety Measures

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

### 5.5.12 Reporting Urgent Safety Measures

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

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

## 5.6 Test Drug Concentration

Serum concentrations of ASP1650 will be measured. Samples will be collected as outlined in the ASP1650 Pharmacokinetic and Immunogenicity Schedule [Table 2]. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory using validated analytical methods. Samples remaining after pharmacokinetic assessments may be

used for additional biomarker analysis described in [Section 5.7.2 Exploratory Biomarker]. Please refer to the Laboratory Manual for more detailed information.

## 5.7 Other Measurements, Assessments or Methods

### 5.7.1 Optional Blood Sample for Banked Pharmacogenomic Sample Analysis

For subjects who signed a separate ICF, an optional whole blood sample for PGx will be collected at C1D1. PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. A sample of whole blood for possible retrospective PGx analysis will be collected and processed. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to a sponsor-designated analytical/storage laboratory. Please refer to the Laboratory Manual for more detailed information

See [Appendix 12.7 Pharmacogenomic (PGx) Analysis With Banked Sample (Optional)] for further details on the banking procedures.

### 5.7.2 Exploratory Biomarker

Tumor tissue and blood/serum/plasma samples described in [Sections 5.7.2.1 Blood, Plasma and Serum Samples and 5.7.2.2 Tumor Tissue Samples for Biomarker Analysis] may be used for research purposes to identify genomic and/or other biomarkers that may be associated with clinical outcome or dynamic changes associated with ASP1650 treatment (in terms of dose, safety, tolerability and efficacy).

Since the identification of exploratory biomarkers that correlate with the efficacy or safety of ASP1650 treatment may continue to evolve as new findings become available, additional analyses related to ASP1650 activity on tumor signaling pathways or clinical outcomes may be conducted. Tumor tissue and blood/serum samples remaining after the specified biomarker assessments (e.g., aliquots of tumor cell RNA or DNA) may be used for re-testing, additional analyses as defined above or developing, and validating assays related to prediction of response or dynamic changes associated with ASP1650 treatment.

The tumor tissue and blood/serum/plasma samples (e.g., aliquots of tumor cell RNA or DNA, peripheral blood mononuclear cells) will be stored at the study sponsors' facility or a contract laboratory facility for up to 15 years after database closure, at which time the samples will be destroyed. The procedures for the collection, handling and shipping of laboratory samples being submitted to the central laboratory will be specified in a laboratory manual.

#### 5.7.2.1 Blood, Plasma and Serum Samples for Biomarker Analysis

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

#### 5.7.2.2 Tumor Tissue Samples for Biomarker Analysis

Formalin fixed paraffin embedded tumor tissue samples will be obtained for all subjects during the screening period. Subjects must have an available tumor specimen in a tissue block or unstained serial slides, or subject must be an appropriate candidate for tumor biopsy and be amenable to undergoing a tumor biopsy during the screening period. If a biopsy is performed, collection from a site other than lymph nodes is preferred.

An optional on-treatment tumor specimen collected ± 7 days of the cycle 4/day 1 visit may be provided. In cases where a pretreatment biopsy was performed, collection of the on-treatment specimen from the same site is preferred.

The investigator, in consultation with other specialists, as needed (e.g., radiology staff) will assess the risk associated with obtaining a tumor tissue sample and determine if the subject is an appropriate candidate for the procedure. Biopsies should be obtained in accordance with institutional policies/guidelines to minimize risk. Procedures requiring general anesthesia should not be performed to obtain a tumor tissue sample; however, if a surgical procedure under general anesthesia is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject. If a tumor biopsy is to be obtained during screening from a lesion that will be classified as 1 of the target lesions, the biopsy should be performed prior to obtaining the baseline scan, if possible. Otherwise, a new baseline scan should be obtained subsequent to the biopsy of the target lesion.

Tumor tissue samples may be analyzed for biomarkers including but not limited to CLDN6 expression, immune cell infiltration, genetic markers and gene/protein expression related to the mechanisms of action of the study drug.

**Tumor Tissue Requirements**

| Visit | Tumor Tissue Requirement |
|---|---|
| Screening | A minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 9* FFPE unstained slides are required. |
| Post-Progression (optional) | A minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 9* FFPE unstained slides are required. |

FFPE: formalin-fixed paraffin embedded

*If ≥ 9 slides cannot be provided, the sponsor should be contacted for further guidance.

## 5.8 Total Amount of Blood

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

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

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

The maximum amount of blood collected is approximately 67 mL in cycle 1. The amount collected in subsequent cycles is less.

# 6 DISCONTINUATION

## 6.1 Discontinuation of Individual Subject(s) From Study Treatment

The study treatment period is a maximum of 12 treatment cycles. A subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The subject will be discontinued from study treatment if any of the following occur:

- Investigator determines it is in the subject's best interest to discontinue study treatment
- Subject develops disease progression based on serum tumor markers or radiological disease progression as assessed by the investigator.
    - If the investigator believes that the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study treatment up to a maximum of 12 treatment cycles.
- Subject starts another systemic chemotherapy, immunotherapy, radiotherapy or other treatment intended for antitumor activity.
- Subject starts other investigational agent or device.
- Subject develops unacceptable toxicity.
- Subject has a delay of study treatment for ≥ 28 days from when the next study treatment was scheduled to be administered. However, restarting study treatment after dosing delay (beyond ≥ 28 days from when the next study treatment was scheduled to be administered) may be allowed based on investigator consultation with, and approval of, the Astellas medical monitor.
- Subject develops inter-current illness that the investigator determines may jeopardize the subject's safety if the subject continues to receive study treatment.
- Significant deviation from the protocol or eligibility criteria as determined by the sponsor.
- Subject declines further treatment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Subject is noncompliant with the protocol based on investigator or medical monitor assessment.

NOTE: If a subject discontinues ASP1650 prior to disease progression per modified RECIST v1.1 and is not receiving any other systemic anti-cancer therapy, the subject must continue to undergo radiological assessments per protocol-specified schedule.

**Study Discontinuation Criteria**

A subject will be discontinued from the study if any of the following occur:

- Subject or legally authorized representative specifically withdraws consent for any further contact.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death (from any cause).
- Study termination by the sponsor.

### 6.1.1 Lost to Follow Up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.

## 6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

## 6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

# 7 STATISTICAL METHODOLOGY

A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database hard lock. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to database lock, a Final Review of Data and TLFs Meeting will be held to allow a review of the clinical study data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, continuous data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum), and frequency and percentage for categorical data. Kaplan-Meier estimates will be provided for time-to-event endpoints. Separate data displays will be provided for the Safety Lead-in phase and phase 2 of the study unless specified otherwise.

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

## 7.1 Sample Size

The sample size for the Safety Lead-in phase is not based on a statistical power calculation. The planned number of up to 18 subjects would provide adequate information for the objectives of the safety cohort.

Simon's optimal 2-stage design [Simon, 1989] will be used for conducting phase 2 of the study. The null hypothesis is that the true ORR is 10%, and the alternative hypothesis is that the true ORR is 25%. The study will be carried out in 2 stages. In stage I, a total number of 13 subjects treated at the RP2D will be evaluated.

If there is 1 or fewer responses among these 13 subjects, the study will be stopped early for futility. Otherwise, an additional 21 subjects will be enrolled in stage II, resulting in a total number sample size of 34. If there are 6 or more responses among these 34 subjects, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 10% and yields the power of 80%.

## 7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in classification specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

### 7.2.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all enrolled subjects. This will be the primary analysis set for efficacy analyses.

### 7.2.2 Per Protocol Set (PPS)

The per protocol set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant non-adherence to the protocol and will be defined in the SAP. The PPS will be a secondary analysis set for efficacy analyses. Select demographic and baseline characteristics may also be summarized for the PPS.

### 7.2.3 Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all subjects who took at least 1 dose of study drug, and will be used for safety analyses.

For the statistical summary of the safety data, the SAF will be used.

### 7.2.4 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) will consist of the subset of the SAF for which at least 1 ASP1650 concentration measurement is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the Classification Specifications and determined in the Classification Meeting. The PKAS will be used for description of pharmacokinetic data.

### 7.2.5 Dose Limiting Toxicity Evaluation Analysis Set (DEAS)

The dose limiting toxicity evaluation analysis set (DEAS) is defined as all subjects in SAF by excluding the subjects who meet the following criterion:

- A subject without a DLT who receives less than the planned ASP1650 dose during the DLT observation period.

DEAS will be used for the analysis of DLT data.

## 7.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by cohort and dose level and overall for FAS and SAF.

### 7.3.1 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all FAS subjects and for subjects in the SAF by cohort, dose level and overall. Similar tables for screening disposition and follow-up disposition will also be presented. All disposition details and dates of first and last evaluations for each subject will be listed.

### 7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be presented in a listing. The frequency of concomitant medications (prescription, over-the-counter and nutritional supplements) will be summarized by cohort and dose level.

### 7.3.3 Medical History

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

## 7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS. The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS. Response assessment will be based on modified RECIST v1.1, RECIST v1.1 alone and serum marker alone.

### 7.4.1 Analysis of Primary Endpoint

#### 7.4.1.1 Objective Response Rate

ORR is defined as the proportion of subjects for each dose level whose best overall response is rated as confirmed CR or PR by modified RECIST v1.1. ORR by dose level will be calculated and its 90% confidence interval will be constructed by Clopper-Pearson method.

#### 7.4.1.2 Sensitivity Analysis

ORR, as assessed by RECIST v1.1, by dose level will be calculated and its 90% confidence interval will be constructed by Clopper-Pearson method.

#### 7.4.1.3 Subgroup Analysis

The following subgroups may be explored:

- Seminoma vs nonseminoma
- Prior lines of therapy: 2 vs ≥ 3
- Primary testicular site vs other (mediastinal or retroperitoneum)
- Presence of visceral metastases: yes vs no
- Late relapse: yes vs no
- Prior high-dose chemotherapy: yes vs no

### 7.4.2 Analysis of Secondary Endpoints

#### 7.4.2.1 Clinical Benefit Rate

CBR is defined as the proportion of subjects for each dose level whose best overall response is rated as confirmed CR, PR or durable SD. Durable SD is a SD maintained for at least 12 weeks. CBR by dose level will be calculated and its 90% confidence interval will be constructed.

#### 7.4.2.2 Duration of Response

DOR will be calculated only for the subgroup with confirmed response CR/PR. The distribution of DOR will be summarized only for subjects receiving the phase 2 dose level using Kaplan-Meier methodology.

#### 7.4.2.3 Progression-free Survival

PFS is defined as the time from the date of first dose until the date of disease progression, or until death due to any cause. If a subject has neither progressed nor died, the subject will be censored at the date of last disease assessment. More detailed censoring algorithm will be provided in the SAP.

The distribution of PFS will be summarized only for subjects receiving the phase 2 dose level using Kaplan-Meier methodology.

## 7.5 Analysis of Safety

### 7.5.1 Dose Limiting Toxicities

A DLT event, as defined in the DLT criteria in [Section 2.2.1 Study Design], will be summarized by cohort and dose level using DEAS. Details of DLTs will be presented in listings and subject narratives.

### 7.5.2 Adverse Events

AEs will be coded using the MedDRA.

TEAE is defined as an AE observed after starting administration of the study drug and up to 30 days after the last dose of study drug.

The number and percentage of subjects with treatment-emergent AEs, SAEs, AEs leading to withdrawal of treatment, and AEs related to study drug will be summarized by System Organ

Class, preferred term, cohort and dose level. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

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

### 7.5.3 Laboratory Assessments

For quantitative laboratory measurements, descriptive statistics will be used to summarize results and change from baseline for subjects in the SAF by cohort, dose level and time point. Shifts from baseline to the worst grade based on NCI-CTCAE during treatment period in laboratory tests will also be tabulated.

Laboratory data will be displayed in listings.

### 7.5.4 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by cohort, dose level and time point.

Potentially clinically significant vital signs will be defined and tabulated as described in the SAP. Vital signs data will be displayed in listings.

### 7.5.5 Routine 12-lead Electrocardiograms

The 12-lead ECG results will be summarized by cohort, dose level and time point. A shift analysis table showing shifts from baseline in overall ECG (normal and abnormal) will be provided.

### 7.5.6 Eastern Cooperative Oncology Group Performance Status

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

## 7.6 Analysis of Pharmacokinetics

Descriptive statistics will include the number of subjects (n), mean, standard deviation, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, maximum.

### 7.6.1 Serum Concentrations

Serum concentrations of ASP1650 will be listed and summarized using descriptive statistics by dose and scheduled time point. Standard graphics including mean serum concentration-time profiles, overlay (spaghetti) plots will be produced.

### 7.6.2 Estimation of Pharmacokinetic Parameters

Noncompartmental (NCA) analysis will be performed to calculate ASP1650 pharmacokinetic parameters using Phoenix version 6.3 or higher [Certara LP, 100 Overlook Center Suite 101, Princeton, NJ 08540, US]. Descriptive statistics will be provided for the NCA-based parameters whenever applicable.

Further details on the calculation of the pharmacokinetic parameters will be provided in the SAP.

## 7.7 Analysis of Biomarkers

Associations between biomarkers [Section 5.7.2 Exploratory Biomarker] and clinical results (efficacy, safety, or, pharmacodynamics) may be performed on subjects in the SAF who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. Biomarkers may be summarized graphically or descriptively as they relate to clinical measures, as applicable. Summary statistics may be tabulated. Additional post hoc statistical analyses may be outlined in the SAP. All analyses described in this section are based on availability of the data.

## 7.8 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.3 Major Protocol Deviations] will be summarized for all enrolled subjects by cohort, dose level and total as well as by site. A data listing will be provided by site and subject.

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

## 7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned during the Safety Lead-in phase. Safety, pharmacokinetic and other clinical data will be reviewed on an ongoing basis.

A futility analysis will be conducted 24 weeks after the first dose of the 13$^{th}$ subject in stage I of phase 2 of the study. The study may be stopped if less than 2 confirmed response (confirmed CR or confirmed PR by modified RECIST v1.1) are observed.

## 7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to determine whether or not an AE is treatment emergent and the medication is concomitant. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

See the SAP for details of the definitions for windows to be used for analyses by visit.

# 8 OPERATIONAL CONSIDERATIONS

## 8.1 Data Collection

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

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at a central laboratory. Central Laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The Central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

All procedures conducted under the protocol must be documented.

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

## 8.2 Screen Failures

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

## 8.3 Major Protocol Deviations

A major protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The major protocol deviation criteria are as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

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

If a major deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

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

# 9 END OF TRIAL

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

Study completion is defined as the conclusion of data collection for the defined study endpoints. The study may be closed within a participating country per local regulations once the study has completed and if all subjects enrolled in the country are no longer receiving study treatment.

# 10 STUDY ORGANIZATION

## 10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB)

No IDMC or DSMB will be utilized for this study.

## 10.2 Other Study Organization

The DEC will be responsible for the review of safety data at specified time points in order to provide an assessment of whether reduction or escalation should occur within the next cohort and/or to determine when MTD has been reached in a given dose level. At each meeting, individual subject data will be reviewed for dose reduction or escalation decisions. Additional details regarding responsibilities and membership requirements will be included in the DEC Charter.

# 11 REFERENCES

Adra N, Einhorn LH, Althouse SK, Ammakkanavar NR, Musapatika D, Albany C, et al. Phase II trial of pembrolizumab in patients with platinum refractory germ-cell tumors: a Hoosier Cancer Research Network Study GU14-206. Ann Oncol. 2018;29(1):209-14.

Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol. 2009;5(5):499-521.

Einhorn, EH. Testicular cancer: an oncological success story. Clin Cancer Res. 1997;3(12):2630-32.

Einhorn LH, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med. 2007;357(4):340-48.

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

Feldman DR, Sheinfeld J, Bajorin DF, Fischer P, Turkula S, Ishill N, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol. 2010; 28(10):1706-13.

Finco D, Grimaldi C, Fort M, Walker M, Kiessling A, Wolf B, Salcedo T, et al. Cytokine release assays: Current practices and future directions. Cytokine. 2014;66:143-155.

Hanna NH, Einhorn LH. Testicular cancer–discoveries and updates. N Engl J Med. 2014;371(21): 2005-16.

Hartmann JT, Einhorn L, Nichols CR, Droz JP, Horwich A, Gerl A, et al. Second-line chemotherapy in patients with relapsed extragonadal nonseminomatous germ cell tumors: results of an international multicenter analysis. J Clin Oncol. 2001;19(6):1641-48.

Kondagunta GV, Bacik J, Donadio A, Bajorin D, Marion S, Sheinfeld J, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol. 2005;23(27):6549-55.

LaCasce AS, Castells MC, Burstein H, Meyerhardt JA. Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy. UpToDate; Literature review current through: Jun 2018. Available at: https://www.uptodate.com/contents/infusion-related-reactions-to-therapeutic-monoclonal-antibodies-used-for-cancer-therapy/print.

Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. Appl Statist. 2015; 64(Part 3):507–23.

Loehrer PJ Sr, Einhorn LH, Williams SD. VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. J Clin Oncol. 1986;4(4):528-36.

Loehrer PJ Sr, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol. 1998;16(7): 2500-04.

Murphy BR, Breeden ES, Donohue JP, Messemer J, Walsh W, Roth BJ, et al. Surgical salvage of chemorefractory germ cell tumors. J Clin Oncol. 1993;11(2):324-29.

National Cancer Institute. Testicular Cancer Treatment (PDQ®)–Health Professional Version: General information about testicular cancer. Available at https://www.cancer.gov/types/testicular/hp/testicular-treatment-pdq. Accessed 16 Jul 2018.

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

Pont J, Bokemeyer C, Harstrick A, Sellner F, Greinix H, Stoiber F. Chemotherapy for germ cell tumors relapsing after high-dose chemotherapy and stem cell support: a retrospective multicenter study of the Austrian Study Group on Urologic Oncology. Ann Oncol. 1997;8(12):1229-34.

Saxman, SB, Nichols CR, and Einhorn LH. Salvage chemotherapy in patients with extragonadal nonseminomatous germ cell tumors: the Indiana University experience. J Clin Oncol. 1994;12(7):1390-93.

Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clin Trials. 1989;10:1-10.

Surveillance, Epidemiology, and End Results (SEER) Stat Database: Cancer Stat Facts: Testicular Cancer (2008-2014). Available at: www.seer.cancer.gov. Accessed 30 Jul 2018.

# 12 APPENDICES

## 12.1 Ethical, Regulatory and Study Oversight Considerations

### 12.1.1 Ethical Conduct of the Study

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation EU No. 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### 12.1.3 Protocol Amendment and/or Revision

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

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

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

### 12.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 12.1.5 Informed Consent of Subjects

#### 12.1.5.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF statement will be reviewed and signed and dated by the subject or his guardian or legal representative, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy of the ICF.

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

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

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

### 12.1.6 Source Documents

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

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

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

### 12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, eCRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

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

### 12.1.8 Subject Confidentiality and Privacy

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

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

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

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

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

### 12.1.9 Arrangement for Use of Information and Publication of the Clinical Study

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

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

### 12.1.10 Signatory Investigator for Clinical Study Report

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

## 12.2 Procedure for Clinical Study Quality Control

### 12.2.1 Clinical Study Monitoring

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

### 12.2.2 Direct Access to Source Data/Documents

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

### 12.2.3 Data Management

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

### 12.2.4 Quality Assurance

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

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

## 12.3 Contraception Requirements

**CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL.**

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

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

## 12.4 List of Excluded Concomitant Medications

The following are a list describes medications. This list should not be considered all inclusive. Consult individual drug labels for specific information. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the sponsor is encouraged.

**Excluded Concomitant Medications**

| Corticosteroids (14 days prior to first dose) | Chemotherapy | Immunotherapy |
|---|---|---|
| bethamethasone<br>dexamethasone<br>hydrocortisone*<br>methylprednisolone<br>prednisone<br>prednisolone<br>triamcinolone | adriamycin<br>bleomycin<br>busulfan<br>carboplatin<br>capecitabine<br>cisplatin<br>docetaxel<br>doxorubicin<br>etoposide<br>fluorouracil<br>idrarubicin<br>leucovorin<br>oxaliplatin<br>trifluridine<br>vinblastine<br>vincristine<br>vinorelbine | ado-trastuzumab emtansine<br>alemtuzumab<br>blinatumomab<br>brentuximab vedotin<br>cetuximab<br>ibritumomab tiuxetan<br>ipilimumab<br>nivolumab<br>pembrolizumab<br>trastuzumab |

* Inhaled, intranasal and topically applied steroids are allowed.

**Cautionary Concomitant Medications**

| Corticosteroids (during study treatment) |
|---|
| bethamethasone<br>dexamethasone<br>hydrocortisone*<br>methylprednisolone<br>prednisone<br>prednisolone<br>triamcinolone |

* Inhaled, intranasal and topically applied steroids are allowed.

## 12.5 Liver Safety Monitoring and Assessment

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

**Definition of Liver Abnormalities**

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

| | **ALT or AST** | | **Total Bilirubin** |
|---|---|---|---|
| **Moderate** | > 3 x ULN | or | > 2 x ULN |
| **Severe** | > 3 x ULN | and | > 2 x ULN |

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

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

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

**Follow-up Procedures**

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

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

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

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

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

**Study Treatment Discontinuation**

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

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or INR > 1.5) (If INR testing is applicable/evaluated).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

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

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant).

The 2 “requirements” for Hy’s Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 x ULN (“2 x ULN elevations are too common in treated and untreated subjects to be discriminating”).
2. Cases of increased total bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert’s syndrome [Temple, 2006].

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

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3 x ULN, 1 or more also show elevation of serum total bilirubintotal bilirubin to > 2 x ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury [Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA in July 2009].

## References

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

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

## 12.6 Common Serious Adverse Events

For this protocol, there is no list of common SAEs anticipated for the study population for the purposes of IND safety reporting.

## 12.7 Pharmacogenomic (PGx) Analysis With Banked Sample (Optional)

### INTRODUCTION

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

### OBJECTIVES

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

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

### SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx substudy. Subjects must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

### SAMPLE COLLECTION AND STORAGE

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

### PGx ANALYSIS

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

### DISPOSAL OF PGx SAMPLES / DATA

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

## INFORMATION DISCLOSURE TO THE SUBJECTS

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

## 12.8 Eastern Cooperative Oncology Group Performance Status Scale

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

# 13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 1

**I. The purpose of this amendment is:**

| **Nonsubstantial Changes** |
|---|
| **1. Increase in Study Period** |
| DESCRIPTION OF CHANGE: |
| The projected study period is extended from 1Q2021 to 3Q2022 |
| |
| RATIONALE: |
| The extension is necessary due to challenges in recruitment of the study specific patient population. |
| |
| **2. Increase in Number of Study Centers** |
| DESCRIPTION OF CHANGE: |
| The number of US study centers participating in this study is increased from 3 to 4. |
| |
| RATIONALE: |
| To expand geographical area for patient population outreach and increase enrollment capabilities. |
| |
| **3. Change to Monitoring of Infusion-related Reactions** |
| DESCRIPTION OF CHANGE: |
| Is added such that subjects who receive ASP1650 and experience a Grade 1 infusion-related reaction (IRR) may be premedicated prior to their next infusion. Text is also added to have subjects monitored during their next infusion. |
| |
| RATIONALE: |
| Pre-medication and monitoring of patients is suggested to minimize the risk of IRRs for subsequent reactions. |
| |
| **4. Change to Management of IRRs** |
| DESCRIPTION OF CHANGE: |
| Text in Table 3 is added to allow for premedication prior to subsequent ASP1650 infusions in those subjects experiencing a previous Grade 1 IRR following ASP1650 infusion. In addition, text is added to closely monitor those patients during their next infusion. |
| |
| RATIONALE: |
| Pre-medication and monitoring is suggested to minimize the risk of IRRs for subsequent infusions. |
| |

| **5. Change to Discontinuation Language** |
|---|
| DESCRIPTION OF CHANGE: |
| Subjects appearing to derive clinical benefit from ASP1650 may now continue treatment for up to 12 treatment cycles. In addition, subjects are allowed to restart study medication after a ≥ 28 day delay based on investigator consultation with, and approval of, the Astellas Medical Monitor |
| |
| RATIONALE: |
| To allow subjects to continue treatment if they are deriving clinical benefit per the investigator's discretion. The allowance for restarting study medication is added as a mitigation strategy during the COVID-19 pandemic as subjects may need to miss visits. |
| |
| **6. Minor Administrative-type Changes** |
| DESCRIPTION OF CHANGE: |
| Include minor administrative-type changes, e.g., typos, format, numbering, personnel update, consistency throughout the protocol. |
| |
| RATIONALE: |
| To provide clarifications to the protocol and to ensure complete understanding of study procedures and to ensure contact details are current. |

## II. Amendment Summary of Changes:

### IIa. Nonsubstantial Changes

| **II Contact Details of Key Sponsor's Personnel** | |
|---|---|
| WAS: | |
| Clinical Research Contacts: | PPD<br>Astellas Pharma Global Development, Inc.<br>1 Astellas Way, Northbrook, Illinois 60062<br>PPD |
| IS AMENDED TO: | |
| Clinical Research Contacts: | PPD<br>Astellas Pharma Global Development, Inc.<br>1 Astellas Way, Northbrook, Illinois 60062 |

| | |
|---|---|
| | PPD |

| **IV Synopsis, Planned Study Period** |
|---|
| WAS: |
| From 1Q2019 to 1Q20212 |
| |
| IS AMENDED TO: |
| From 1Q2019 to ~~1Q2021~~ **3Q2022** |

| **IV Synopsis, Planned Total Number of Study Centers and Location(s)** |
|---|
| WAS: |
| Approximately 3 centers in the United States |
| |
| IS AMENDED TO: |
| Approximately ~~3~~ **4** centers in the United States |

| **IV Synopsis, Study Treatment Discontinuation Criteria and 6 Discontinuation**<br>*6.1 Discontinuation of Individual Subject(s) From Study Treatment* |
|---|
| WAS: |
| • Subject develops disease progression based on serum tumor markers or radiological disease progression as assessed by the investigator.<br>  ○ If the investigator believes that the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study treatment until an additional radiologic assessment is completed (≤ 6 weeks from previous radiologic assessment). If upon subsequent serum tumor markers or radiologic assessment subject has disease progression per modified RECIST v1.1 criteria, as assessed by the investigator, the subject will discontinue study treatment; if assessed as stable disease by the investigator, they may remain on treatment.<br>• Subject has a delay of study treatment for ≥ 28 days from when the next study treatment was scheduled to be administered. |
| |
| IS AMENDED TO: |
| • Subject develops disease progression based on serum tumor markers or radiological disease progression as assessed by the investigator.<br>  ○ If the investigator believes that the subject is continuing to derive clinical benefit (asymptomatic and/or without worsening of performance status or overall health) |

from study treatment, and an increase in tumor burden is not likely to affect vital organ function, the subject may remain on study treatment ~~until an additional radiologic assessment is completed (≤ 6 weeks from previous radiologic assessment). If upon subsequent serum tumor markers or radiologic assessment subject has disease progression per modified RECIST v1.1 criteria, as assessed by the investigator, the subject will discontinue study treatment; if assessed as stable disease by the investigator, they may remain on treatment~~ **up to a maximum of 12 treatment cycles**.

- Subject has a delay of study treatment for ≥ 28 days from when the next study treatment was scheduled to be administered. **However, restarting study treatment after dosing delay (beyond ≥ 28 days from when the next study treatment was scheduled to be administered) may be allowed based on investigator consultation with, and approval of, the Astellas medical monitor.**

**1 Introduction**
***1.4 Risk Benefit Assessment***

WAS:

Based on currently available clinical data, ASP1650 was well-tolerated and most observed AEs have been manageable. Potential risks of ASP1650 are hypersensitivity, including IRRs, and effects on pancreatic tissue and platelets. Subjects receiving ASP1650 do not require premedication for prevention of HSRs and IRRs; however, subjects should be closely monitored for IRRs to facilitate early identification and management. The other potential risks associated with ASP1650 can be managed by monitoring amylase, lipase, and platelet levels.

IS AMENDED TO:

Based on currently available clinical data, ASP1650 was well-tolerated and most observed AEs have been manageable. Potential risks of ASP1650 are hypersensitivity, including IRRs, and effects on pancreatic tissue and platelets. Subjects receiving ASP1650 ~~do not require premedication~~ **who experience an IRR during or after infusion may be premedicated prior to their next infusion and closely monitored** for prevention of HSRs and IRRs~~; however, subjects should be closely monitored for IRRs to facilitate early identification and management~~. The other potential risks associated with ASP1650 can be managed by monitoring amylase, lipase, and platelet levels.

**2 Study Objectives, Design, and Endpoint(s)**
***2.2.1 Study Design***

WAS:

This is a phase 2, open-label, single-arm, multicenter study to assess the safety and efficacy of ASP1650, an mAb targeting CLDN6, in male subjects with incurable platinum refractory germ cell tumors. Up to 46 subjects at approximately 3 centers located in the United States will participate in the study.

| IS AMENDED TO: |
|---|
| This is a phase 2, open-label, single-arm, multicenter study to assess the safety and efficacy of ASP1650, an mAb targeting CLDN6, in male subjects with incurable platinum refractory germ cell tumors. Up to 46 subjects at approximately ~~3~~ **4** centers located in the United States will participate in the study. |

| **5 Treatments and Evaluation**<br>***5.1.2.2 ASP1650 Interruption or Permanent Discontinuation*** |
|---|
| WAS: |
| There is a +5 day allowable window for dosing ASP1650 (with the exception of C1D1). If ASP1650 treatment is delayed more than 2 days then it should be administered as soon as the reason for delay has resolved, which will then become day 1 of the next cycle. Permanently discontinue ASP1650 treatment if delayed beyond 28 days from when the next study treatment was scheduled to be administered. |
| |
| IS AMENDED TO: |
| There is a +5 day allowable window for dosing ASP1650 (with the exception of C1D1). If ASP1650 treatment is delayed more than 2 days then it should be administered as soon as the reason for delay has resolved, which will then become day 1 of the next cycle. Permanently discontinue ASP1650 treatment if delayed beyond 28 days from when the next study treatment was scheduled to be administered. **However, restarting study treatment after dosing delay (beyond ≥ 28 days from when the next study treatment was scheduled to be administered) may be allowed based on investigator consultation with, and approval of, the Astellas medical monitor.** |

| **5 Treatments and Evaluation**<br>*5.1.2.3 Guidelines for Infusion-Related Reactions for ASP1650* |
|---|
| WAS: |
| Table 3 Infusion-Related Reactions |

| Infusion-Related Reactions | |
|---|---|
| CTCAE Grade | Management |
| Grade 1 standard infusion reaction | Continue infusion and closely monitor the subject. |

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

| |
|---|
| IS AMENDED TO: |
| Table 3 Infusion-Related Reactions |

| Infusion-Related Reactions | |
|---|---|
| CTCAE Grade | Management |
| Grade 1 standard infusion reaction | Continue infusion and closely monitor the subject.<br>**For the next infusion:** |

| | |
|---|---|
| | • **Pre-medicate as appropriate.*** <br> • **Closely monitor the subject for symptoms and signs of an infusion reaction.** |

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

# 14 SPONSOR'S SIGNATURES