A Phase 1, Open-label Study of ASP1948, Targeting an Immune Modulatory Receptor, in Japanese Patients with Advanced Solid Tumors

ISN/Protocol 1948-CL-0102

Version 2.1

Incorporating Non Substantial Amendment 3 [See Attachment 1]

<08/Sep/2021>

Sponsor:

Astellas Pharma Inc.

2-5-1, Nihonbashi-Honcho, Chuo-ku,
Tokyo 103-8411, Japan

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Feb 13, 2020 (2.0 version)

Sep 08, 2021 (2.1 version)

Table of Contents

SIGNATURES

1. AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This study will be conducted in adherence to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable laws and regulatory requirements, as well as this protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement by signature or "printed name and seal."

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

Contact information for the Sponsor:

Corporate name: Astellas Pharma Inc.

Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8411, Japan

Telephone number: PPD

Sponsor's personnel: PPD

[Contact numbers during non-business hours and for emergency]:

Telephone number: PPD

PPD

Contact information for the contract research organization (CRO):

Corporate name: PPD

PPD

Corporate name: PPD

CRO's personnel: PPD

[Contact numbers during non-business hours and for emergency]:

Telephone number: PPD

24-hour Contact for Serious Adverse Events See [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]	**Please fax or email JUTOKUNA YUUGAIJISHOU HOUKOKUSHO to:** Astellas Pharma Inc. Japan Pharmacovigilance Fax number: +81-(0)3-3243-5747 Email: rk-safety-jp@astellas.com
Medical Monitors	PPD Astellas Pharma Global Development, Inc. (APGD) 1 Astellas Way, Northbrook, Illinois 60062 US PPD PPD
Clinical Research Contact	PPD Astellas Pharma Inc. Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-8411, Japan PPD

1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	08 Sep 2021 Version 2.1
Sponsor: Astellas Pharma Inc. (API)	**Protocol Number:** 1948-CL-0102
Compound Name: ASP1948	**Phase of Development:** Phase 1
Title of Study: A Phase 1, Open-label Study of ASP1948, Targeting an Immune Modulatory Receptor, in Japanese Patients with Advanced Solid Tumors	
Planned Study Period: From 3Q2019 to 2Q2022.	

Study Objective(s) and Endpoint(s):

Objective(s)	**Endpoint(s)**
Primary	
• To evaluate the tolerability and safety profile of ASP1948 in Japanese patients with locally advanced (unresectable) or metastatic solid tumors.	• Safety and tolerability as noted by the following: dose limiting toxicities (DLTs), adverse events (AEs), immune-related AEs (irAEs), infusion-related reactions (IRRs), serious adverse events (SAEs), laboratory test results (complete blood count [CBC], serum chemistry, urinalysis, prothrombin time/international normalized ratio [PT/INR], activated partial thromboplastin time [aPTT], thyroid stimulating hormone [TSH] and free thyroxine [free T4]), electrocardiograms (ECGs), vital signs, physical exams and Eastern Cooperative Oncology Group (ECOG) Performance Status.
• To characterize the pharmacokinetic profile of ASP1948 in Japanese patients.	• Pharmacokinetic parameters (AUC_{last}, AUC_{inf} [and %extrap], AUC_{tau}, C_{max}, C_{trough}, t_{max}, $t_{½}$, t_{last}, CL, and V as applicable) of ASP1948.
Secondary	
• To evaluate the antitumor effect of ASP1948.	• Sum of diameters (SOD) for the subjects with at least 1 measurable lesion, which is defined as the sum of all target lesions at a tumor assessment. • Best overall response (BOR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and "immune" Response Evaluation Criteria in Solid Tumors (iRECIST).
Exploratory	
• To evaluate the immunogenicity of ASP1948.	• Immunogenicity of ASP1948 as measured by the frequency of antidrug antibody (ADA) positive subjects.
• To evaluate target engagement of ASP1948.	• Determination of ASP1948 target engagement by analysis of receptor occupancy on peripheral blood mononuclear cells in subjects treated with ASP1948.
• To evaluate pharmacodynamic activities of ASP1948.	• Pharmacodynamic effects of ASP1948.
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome of ASP1948.	• Exploratory analysis of potential biomarkers of ASP1948 activity.

Planned Total Number of Study Sites and Location(s):

1 study site in Japan

Study Population:

Japanese patients with locally advanced (unresectable) or metastatic solid tumor malignancies who have received prior therapy.

Number of Subjects to be Enrolled/Randomized:

Approximately 18 subjects (6 subjects per dose level).

Study Design Overview:

This is a phase 1, open-label study of ASP1948, a fully human monoclonal immunoglobulin G4 antibody with the S228P hinge stabilization that targets neuropilin-1 expressing intratumoral regulatory T cell (Tregs) affecting their stability/viability and hindering their suppression function. This study consists of 3 dose levels (Dose level A: ASP1948, 1200 mg for once every 2 weeks [Q2W]; Dose level B: ASP1948, 2000 mg Q2W; and Dose level C: ASP1948, 3000 mg for once every 3 weeks [Q3W]) and enrollment of subjects into Dose level A will take place first. Dose level B would only be opened if Dose level A is deemed tolerable. Dose level C would only be opened if Dose level B is deemed tolerable.

Study Periods (Figure 1)

The study consists of 2 periods: Screening (up to 28 days) and treatment period. The DLT observation period is set at the beginning of the treatment period of each dose level. A subject can continue to participate in the study after the end of the DLT observation period until discontinuation criteria are met. After discontinuation of investigational product (IP), all subjects will complete an End of Treatment visit, along with 30-day and 90-day safety follow-up visits from the last dose of IP. The 90-day safety follow-up visit is optional for subjects who discontinue due to progressive disease or initiate new anticancer treatment after the last dose of IP.

Definitions of Cycle and DLT Observation Period

A cycle is defined as 14 days (2 weeks) for Dose level A and Dose level B, or 21 days (3 weeks) for Dose level C. Dosing occurs on Day 1 of every cycle. The DLT observation period will be 28 days for Dose level A and Dose level B, or 21 days for Dose level C. Note that the DLT observation period is from Cycle 1 Day 1 to Cycle 2 Day 14 for Dose level A and Dose level B, or from Cycle 1 Day 1 to Cycle 1 Day 21 for Dose level C.

The DLT observation period may be extended if deemed appropriate by the Dose Escalation and Safety Committee (DESC), consisting of sponsor representatives, principal investigator and/or subinvestigators and statistical advisor.

Tolerability Evaluation Procedures

The tolerability of ASP1948 at 1200 mg Q2W (Dose level A), 2000 mg Q2W (Dose level B) and 3000 mg Q3W (Dose level C) will be assessed during the DLT observation period. Subjects will be enrolled first into Dose level A, and then only if Dose level A is determined to be tolerable, Dose level B would be opened. Dose level C would be opened if Dose level B is determined to be tolerable. In principle, 3 subjects will initially be enrolled at each dose level. Any of the ASP1948 related AEs specified as DLTs as defined in the "DLT Criteria" will be assessed during the DLT observation period. Quantitative assessment of DLTs will be performed according to the criteria referring to the Bayesian Optimal Interval (BOIN) Design [Liu et al, 2015] with the target DLT rate of 0.33 and optimal interval of (0.260, 0.395). The following table shows the recommended actions in the cases of 3 to 9 evaluable subjects for DLT assessment. The maximum number of subjects at a dose level is 9.

Recommended Action from the Number of Subjects for DLT Assessment

	Number of Subjects evaluable for DLT Assessment				
Recommended Action	**3**	**4****	**5****	**6**	**9**
[Tolerable] If the number of subjects with DLTs is the number given in the right cell or less, the dose can be determined to be tolerable.	0	1	1	1	2
[Stay] If the number of subjects with DLTs is equal to the number given in the right cell, enrollment is continued.	1	-	-	2*	3*
[Not tolerable] If the number of subjects with DLTs is the number given in the right cell or more, the dose is determined to be intolerable.	2	2	2	3	4

DESC: Dose Escalation and Safety Committee; DLT: dose limiting toxicity

* In case the number of subjects for DLT assessment is 6 and 9, if the recommended action is Stay, the tolerability of the dose will be assessed comprehensively at the DESC. According to a decision at the DESC, additional 3 subjects may be enrolled to continue the tolerability assessment in case the number of subjects for DLT assessment is 6.

** In case the number of subjects for DLT assessment is 4 or 5, it is considered exceptional, including, for example, if informed consent is obtained from more than 3 subjects in the process of enrolling the initial 3 subjects. In such a case, these subjects will be included for the initial DLT assessment.

DESC will be held after the end of the DLT observation period for all subjects enrolled in each dose level. The sponsor will comprehensively assess the data (including AEs reported for subjects who are unevaluable for DLT), and discuss the tolerability of the current dose with the principal investigator and/or subinvestigators and statistical advisor at the DESC. Based on the results of the discussion, the sponsor will decide the tolerability of the current dose level. Detailed procedures will be provided in a separately prepared procedure manual.

DLT Criteria

A DLT is defined as any of the following AEs (graded using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]Version 4.03) that the investigator (or sponsor) cannot clearly attribute to a cause other than IP:

- 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 nonhematological AE (excluding asymptomatic changes to amylase, lipase and hypophosphatemia)
- Grade ≥ 2 pneumonitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN; Grade ≥ 3) in subjects without liver metastases
- AST or ALT > 8 × ULN in subjects with liver metastases
- AST or ALT > 3 × ULN and total bilirubin (TBL) > 2 × ULN (in subject with Gilbert's syndrome: AST or ALT > 3 × ULN and direct bilirubin > 1.5 × ULN)
- TBL > 3 × ULN (Grade ≥ 3)
- Grade ≥ 2 encephalopathy, meningitis or Grade ≥ 2 motor or sensory neuropathy

- Grade ≥ 2 pulmonary or central nervous system (CNS) hemorrhage
- Grade ≥ 3 hemorrhage
- Any grade arterial thrombotic event (angina, myocardial infarction, transient ischemic attack [TIA], cerebrovascular accident [CVA] and any other arterial thromboembolic event)
- Any grade gastrointestinal perforation
- Any grade wound dehiscence
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- IRR that requires the infusion to be discontinued

Febrile neutropenia, thrombocytopenia accompanied by bleeding that requires any transfusion, and anemia requiring transfusion regardless of grade, may be considered DLTs by the investigator (or sponsor). In addition, in case the second and/or third dose for Dose level A and Dose level B or the the second dose for Dose level C cannot be performed within 7 days after a scheduled visit for drug related toxicities not specified in the above bullet list, this may be also considered DLTs by the investigator (or sponsor).

Subjects who are tolerating IP at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review by the DESC.

Replacement of Subjects

A subject without a DLT who receives less than the prescribed ASP1948 dose during the DLT observation period, or does not complete the DLT observation period for a reason other than DLT (e.g., consent withdrawal), will not be DLT evaluable and may be replaced.

Intra-subject Dose Escalation (Dose level A only)

For subjects in Dose level A, intra-subject dose escalation is allowed in the judgment of the investigator, in subjects who did not experience a DLT, if Dose level B (ASP1948, 2000 mg) is deemed tolerable at the DESC.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Institutional review board (IRB)-approved written informed consent must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is ≥ 20 years of age at the time of signing informed consent.
3. Subject has locally advanced (unresectable) or metastatic solid tumor malignancy (no limit to the number of prior treatment regimens) that is confirmed by available pathology records or current biopsy (if needed) and has received all standard therapies (unless the therapy is contraindicated or intolerable) felt to provide clinical benefit in the opinion of the treating investigator for his/her specific tumor type.
4. Subject has an ECOG Performance Status of 0 or 1.
5. Subject's last dose of prior antineoplastic therapy, including any immunotherapy, was at least 21 days prior to initiation of IP administration. A subject with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutation-positive non-small cell lung cancer (NSCLC) is allowed to remain on EGFR tyrosine kinase inhibitor (TKI) or ALK inhibitor therapy until 4 days prior to initiation of IP administration.
6. Subject has completed any radiotherapy (including stereotactic radiosurgery) at least 14 days prior to initiation of IP administration.
7. Subject with metastatic castration resistant prostate cancer (mCRPC) (positive bone scan and/or soft tissue disease documented by computed tomography [CT]/magnetic resonance imaging [MRI]) meets both of the following:
   - Subject has serum testosterone ≤ 50 ng/dL at Screening.

- Subject has had an orchiectomy or plans to continue androgen deprivation therapy (ADT) for the duration of study treatment.

8. Subject has adequate organ function as indicated by the following laboratory values within 7 days prior to initiation of IP administration. (If a subject has received a recent blood transfusion, the laboratory tests must be obtained ≥ 28 days after any blood transfusion.) Note: Growth factors, colony stimulating factors are not permitted in the screening period.

Parameter	Laboratory Value
Hematological	
ANC	≥ 1500/µL
Platelets	≥ 100,000/µL
Hemoglobin	≥ 9 g/dL
Renal	
Creatinine	Either a) ≤ institutional ULN, or b) eGFR* ≥ 45 mL/min/1.73m^2 if creatinine is > ULN *Using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (2009); online calculator: https://www kidney.org/professionals/kdoqi/gfr_calculator
Hepatic	
Total bilirubin	Either: a) ≤ 1.5 × ULN, or b) Direct bilirubin ≤ ULN **and** TBL < 3 × ULN (for subjects with Gilbert's syndrome)
AST and ALT	≤ 2.5 × ULN
Coagulation	
INR	Either: a) ≤ 1.5 × ULN for subjects not receiving anticoagulants, or b) within desired therapeutic range for subjects receiving anticoagulants
aPTT	Either: a) ≤ 1.5 × ULN for subjects not receiving anticoagulants, or b) within desired therapeutic range for subjects receiving anticoagulants

ALT: alanine aminotransferase; ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; INR: international normalized ratio; TBL: total bilirubin; ULN: upper limit of normal

9. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
   - Not a woman of childbearing potential (WOCBP; see [Appendix 12.3 Contraception Requirements])
   - WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent throughout the treatment period and for at least 6 months after the final study treatment administration.
10. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 6 months after the final study treatment administration.
11. Female subject must not donate ova starting at first dose of IP and throughout the study period, and for 6 months after the final study treatment administration.
12. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Appendix 12.3 Contraception Requirements])

throughout the treatment period and for at least 6 months after the final study treatment administration.

13. Male subject must not donate sperm during the treatment period and for 6 months after the final study treatment administration.
14. Male subject with a pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 6 months after the final study treatment administration.
15. Subject agrees not to participate in another interventional study while receiving study treatment in the present study (subjects who are currently in the follow-up period of an interventional clinical study are allowed).

Exclusion Criteria:

1. Subject weighs < 45 kg at Screening.
2. Subject has received investigational therapy within 21 days prior to start of IP. (A subject with EGFR activating mutations or a subject with an ALK mutation is allowed to remain on an investigational EGFR TKI or ALK inhibitor until 4 days prior to initiation of IP administration.)
3. Subject requires or has received systemic steroid therapy or any other immunosuppressive therapy within 14 days prior to IP administration. Subjects using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone, 2 mg per day of dexamethasone or up to 10 mg per day of prednisone) are allowed. Note: Corticosteroids for prophylaxis (e.g., contrast dye allergy) or for brief treatment of conditions not related to study treatment (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is also allowed.
4. Subject has symptomatic CNS metastases or subject has evidence of unstable CNS metastases even if asymptomatic (e.g., progression on scans). Subjects with previously treated CNS metastases are eligible, if they are clinically stable and have no evidence of CNS progression by imaging for at least 28 days prior to start of study treatment and are not requiring immunosuppressive doses of systemic steroids (> 30 mg per day of hydrocortisone, > 2 mg per day of dexamethasone or > 10 mg per day of prednisone or equivalent) for longer than 14 days.
5. Subject has leptomeningeal disease as a manifestation of the current malignancy.
6. Subject has an active autoimmune disease. Subjects with type 1 diabetes mellitus, stable endocrinopathies maintained on appropriate replacement therapy and skin disorders (e.g., vitiligo, psoriasis or alopecia) not requiring systemic treatment are allowed.
7. Subject was discontinued from prior immunomodulatory therapy due to a Grade ≥ 3 toxicity that was mechanistically related (e.g., immune-related) to the agent in the judgment of the investigator.
8. Subject has known history of serious hypersensitivity reaction to a known ingredient of ASP1948 or severe hypersensitivity reaction to treatment with another monoclonal antibody.
9. Subject is positive for Hepatitis B virus (HBV) antibodies and surface antigen (including acute HBV or chronic HBV) or Hepatitis C virus ([HCV] RNA). Hepatitis C RNA testing is not required in subjects with negative Hepatitis C antibody testing. HBV antibodies are not required in subjects with negative Hepatitis B surface antigen (HBsAg).
10. Subject has received a live vaccine against infectious diseases within 28 days prior to initiation of study treatment.
11. Subject has a history of drug-induced pneumonitis (interstitial lung disease) or currently has pneumonitis.
12. Subject has an active infection requiring systemic therapy (e.g., intravenous antibiotics) within 14 days prior to IP treatment.
13. Subject is expected to require another form of antineoplastic therapy while on study treatment.

14. Subject has an uncontrolled intercurrent illness including, but not limited to cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements.
15. Subject's AEs (excluding alopecia) from prior therapy have not improved to Grade 1 or baseline within 14 days prior to start of study treatment.
16. Subject has significant cardiovascular disease including:
    - Subject has inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).
    - Subject has a history of myocardial infarction or unstable angina within 6 months prior to Cycle 1 Day 1.
    - Subject has New York Heart Association Class II or greater chronic heart failure.
    - History of CVA or TIA within 6 months prior to study treatment.
    - Subject has significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to study treatment.
17. Subject has a history of hemoptysis (bright red blood of 2 mL or more per episode) within 12 weeks prior to study treatment.
18. Subject has evidence of a bleeding diathesis or significant coagulopathy.
19. Subject has inadequate recovery from prior surgical procedure or has had a major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to study treatment, or anticipates the need for a major surgical procedure during the course of the study or minor surgery within 7 days of starting study treatment.
20. Subject has initiated new treatment with medications that affect the coagulation cascade with an INR ≥ 2 such as vitamin K antagonists, heparins and direct thrombin inhibitors or the use of factor Xa inhibitors within 28 days prior to the start of study treatment. Note: If the subject started receiving such medications more than 28 days prior to the start of study treatment and needs to continue, this is allowed. However, new anticoagulation may not be initiated within 28 days prior to the start of study treatment.
21. Subject has any condition that, in the investigator's opinion, makes the subject unsuitable for study participation.

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

Investigational Product(s):

Name:

ASP1948

Use:

Test product

Dose(s):

Drug	Dose level	Dose (mg)	Dosing Schedule
ASP1948	A	1200	Q2W
	B	2000	Q2W
	C	3000	Q3W

Q2W: once every 2 weeks; Q3W: once every 3 weeks

For subjects in Dose level A who did not experience a DLT, intra-subject dose escalation is allowed in the judgment of the investigator if Dose level B (ASP1948 2000 mg) is deemed tolerable at the DESC.

Mode(s) of Administration:

ASP1948 will be administered intravenously on Day 1 of every 2-week cycle for Dose level A and Dose level B, or on Day 1 of every 3-week cycle for Dose level C.

Dose Modifications:

IP-related toxicity can result in the interruption or discontinuation of IP based on the discretion of the investigator.

Toxicities Requiring Permanent Discontinuation of ASP1948 Treatment

ASP1948 treatment will be permanently discontinued for the following toxicities that are assessed as related to ASP1948, if there is a reasonable possibility that the event may have been caused by ASP1948:

- Hematological toxicity requiring ASP1948 treatment interruption that does not recover to Grade 0 or 1 within 4 weeks
- AST or ALT > 5 × ULN (Grade ≥ 3) in subjects without liver metastases
- AST or ALT > 8 × ULN in subjects with liver metastases
- AST or ALT > 3 × ULN and TBL > 2 × ULN (in subject with Gilbert's syndrome: AST or ALT > 3 × ULN and direct bilirubin > 1.5 × ULN)
- TBL > 3 × ULN
- Grade ≥ 3 nonhematological AE except for Grade 3 rash that has improved to Grade 0 or 1 or Grade ≥ 3 endocrinopathies that are managed to Grade 0 or 1 with replacement therapy.
- Persistent Grade ≥ 2 AEs requiring ASP1948 interruption that do not recover to Grade 0 or 1 within 12 weeks after the last dose with steroid treatment tapered to physiological replacement doses (≤ 10 mg prednisone or equivalent) of study treatment. However, subjects with a persistent Grade ≥ 2 AE requiring ASP1948 interruption may continue on study treatment if asymptomatic and controlled, with investigator and sponsor agreement
- Grade ≥ 2 pneumonitis
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- Grade ≥ 2 encephalopathy, meningitis or Grade ≥ 2 motor or sensory neuropathy
- Any toxicity that results in the inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Grade 3 or 4 IRRs

Toxicities Requiring ASP1948 Treatment Interruption

ASP1948 treatment will be withheld for the following toxicities if there is a reasonable possibility that the event may have been caused by ASP1948:

- 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 rash or Grade 3 endocrinopathies
- AST or ALT ≥ 3.0 and ≤ 5.0 × ULN or TBL > 1.5 and ≤ 3× ULN (in subject with Gilbert's syndrome: AST or ALT ≥ 3.0 and ≤ 5.0 × ULN or direct bilirubin > ULN) in subjects without liver metastases
- AST or ALT ≥ 3.0 and ≤ 8.0 × ULN or TBL > 1.5 and ≤ 3 × ULN (in subjects with Gilbert's syndrome: AST or ALT ≥ 5.0 and ≤ 8.0 × ULN or direct bilirubin > ULN) in subjects with liver metastases
- Any Grade 2 or higher irAE (including but not limited to those listed below):
  - colitis or diarrhea
  - hypophysitis
  - adrenal insufficiency
  - nephritis
  - ocular inflammatory toxicity

- pancreatitis
- new-onset neurological symptoms or signs (other than Grade 2 or higher encephalopathy, meningitis or Grade 2 or higher motor or sensory neuropathy, which require permanent discontinuation of ASP1948 treatment)
- IRR

Additionally, ASP1948 treatment may be interrupted for any AE, laboratory abnormality or intercurrent illness that in the judgment of the investigator warrants delaying dosing of ASP1948 treatment.

Criteria for Resuming Study Treatment

Dosing may be delayed for up to 12 weeks from the end of the prior treatment cycle for recovery of toxicity requiring IP treatment interruption. IP treatment may be resumed if the AEs have recovered to Grade 0 or 1 and steroid treatment tapered to physiological replacement doses (≤ 10 mg per day prednisone or equivalent) and do not meet the criteria for permanent discontinuation of study treatment. Interruption for COVID-19-related illness is limited to 12 weeks. Study treatment may be resumed in the absence of COVID-19-related symptoms per investigator judgement.

Concomitant Treatment (Medication and Nonmedication Therapy) Restrictions or Requirements:

- *Investigational agents:* The use of investigational agents is not allowed during study treatment.
- *Steroids and other immunosuppressive therapy:* The use of immunosuppressive agents and immunosuppressive doses of systemic steroids (> 30 mg/day of hydrocortisone, > 10 mg/day of prednisone, > 2 mg/day of dexamethasone or equivalent) is not allowed during study treatment unless needed to manage AEs related to study treatment. The use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption) is allowed. Physiologic replacement doses of systemic corticosteroids (≤ 30 mg/day of hydrocortisone or ≤ 10 mg/day of prednisone or equivalent) are permitted. Corticosteroids for prophylaxis (e.g., contrast dye allergy) or for brief treatment of conditions not related to study treatment (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is also allowed.
- *Vaccines:* Live vaccines are prohibited while the subject is receiving study treatment and for 14 days after last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, Bacillus Calmette-Guerin (BCG) and typhoid vaccine.
- *Other Anticancer treatment:* The use of other anticancer therapy (e.g., chemotherapy, hormonal therapy, immunotherapy, radiotherapy, biological therapy and targeted therapy) is not allowed during study treatment; however, (1) subjects with mCRPC who do not have orchiectomy should continue ADT during the study and (2) subjects with breast cancer on endocrine or human EGFR 2 therapy should continue those therapies during the study.

  Palliative (limited field) radiation therapy for bone metastases is allowed. Study treatment should be interrupted during radiation therapy. The use of bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors for bone metastases are allowed if initiated prior to study entry.

  Surgical treatment of isolated or symptomatic lesions for palliation or curative management is also allowed.
- *Other:* Hematopoietic factor products used for primary prevention (only prohibited during the DLT observation period).

Duration of Treatment:

Subjects will receive ASP1948 intravenous infusion until treatment discontinuation criteria is met from Cycle 1 Day 1.

Treatment Discontinuation Criteria:

A subject must discontinue study treatment for any of the following reasons:

- Disease progression, as defined by the following:
- Confirmed disease progression by iRECIST ("immune" confirmed progressive disease [iCPD])
- Disease progression by RECIST 1.1 (i.e., unconfirmed progression by iRECIST, denoted "immune unconfirmed progressive disease [iUPD]") and the subject is not clinically stable to await subsequent confirmatory scan
- Clinical Disease Progression per investigator's assessment
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AEs
- Subject requests to stop treatment
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject
- Subject is lost to follow-up
- Female subject becomes pregnant
- Subject remains noncompliant with the protocol based on the investigator's or sponsor's assessment
- A subject who has a confirmed complete response (CR) by 2 scans ≥ 4 weeks apart and who has been on study treatment for at least 12 cycles for Dose level A and Dose level B, or 8 cycles for Dose level C may discontinue study treatment at the discretion of the investigator after receiving at least 2 doses beyond the initial determination of CR
- Treatment interruption of > 12 weeks from the end of the prior treatment cycle
- Subject completes the 2-year treatment period

Statistical Methods:

Sample Size Justification:

The sample size for this study is not based on a statistical power calculation but is expected to provide safety and pharmacokinetic information to determine the tolerability of ASP1948. The estimated number of evaluable subjects is 18 (6 subjects per dose level) for this study. The number of subjects enrolled will be dependent on the DLT incidence. The maximum number of evaluable subjects is 27 (9 subjects per dose level).

Efficacy:

BOR as per RECIST 1.1 and iRECIST will be listed. For the subjects with at least 1 measurable lesion, percentage change of SOD at post baseline assessment visit from SOD at baseline will be presented as a spider plot and best percentage change of SOD will be presented as a waterfall plot.

Safety:

All DLT incidences will be summarized by dose level. The frequency of AEs and SAEs will be summarized by SOC and preferred term. AEs will be coded to SOC and preferred term using MedDRA terminology. Summary statistics will also be provided for laboratory parameters, vital signs, drug exposure and other safety parameters.

Pharmacokinetics:

Descriptive statistics will be used to summarize serum concentrations and pharmacokinetic parameters of ASP1948 where applicable. Individual (spaghetti) and mean concentration-time curves on linear and semilogarithmic scales will be provided as appropriate.

Pharmacodynamics | Immunogenicity:

Descriptive statistics will be provided for pharmacodynamics and immunogenic parameters of ASP1948 whenever applicable. Exploratory analysis of the relationship between pharmacodynamics measurements and pharmacokinetics, efficacy and safety profile in subjects may be performed.

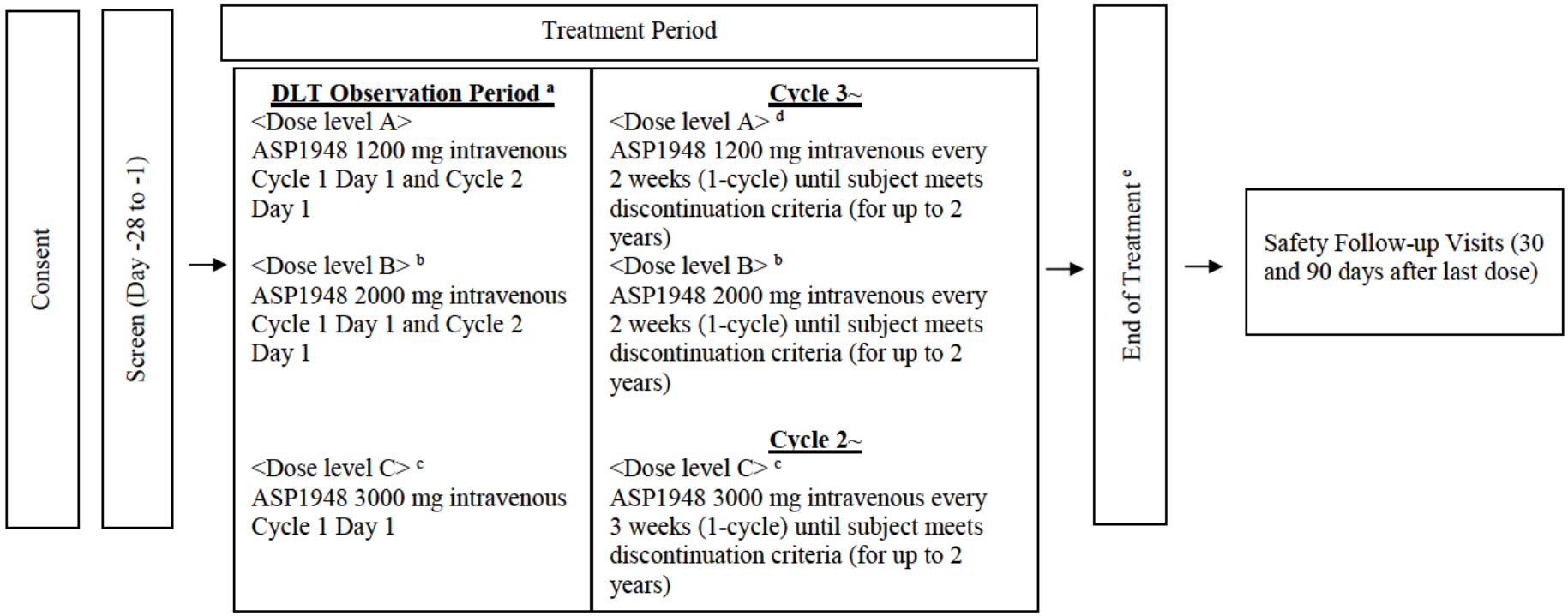
The potential relationship between immunogenicity and pharmacokinetics, efficacy and safety profile in subjects will be assessed.

Interim Analyses:

No formal interim analysis will be performed in this study.

1.2 Study Schema

Figure 1 Study Schema



DLT: dose limiting toxicity
a. The DLT observation period will be 28 days for Dose level A and Dose level B, or 21 days for Dose level C.
b. Dose level B would only be opened if Dose level A is deemed tolerable.
c. Dose level C would only be opened if Dose level B is deemed tolerable.
d. Subjects assigned to Dose level A (ASP1948, 1200 mg) are allowed to dose escalate to 2000 mg (if it is deemed tolerable) at the discretion of the investigator provided the subject did not experience a DLT.
e. End of Treatment visit will occur within 7 days of last dose or decision by the investigators to discontinue the subject from study treatment.

1.3 Schedule of Assessments

Table 1 Schedule of Assessments for Dose level A and Dose level B

Assessments	Screening	Treatment Period								Follow-up	
		Cycle 1				Cycle 2[a]		Cycles 3~	End of Treatment	Safety Follow-up	
Cycle Day	-28 to -1	1	2	3	8	1	8	1		30 days from last dose	90 days from last dose [b]
Visit Window (Days) [c]	0	0	0	0	0	+ 1	+ 1	± 3 [s]	+ 7	+ 3	± 7
General Study Procedures											
Informed Consent	X										
Verify Inclusion/Exclusion	X	X									
Medical History/Disease History/Demographics	X										
Height	X										
Weight	X	X				X		X	X		
Vital Signs	X	X [d]			X	X [d]	X	X [d]	X	X	X
Physical Examination (including auscultation) [e]	X	X			X	X		X	X		
ECOG Performance Status	X	X				X		X	X	X	
Prior/Concomitant Medications [f]	Every visit										
AE Assessment [g]	Every visit										X
Blood Collection											
Hepatitis B and C Testing [h]	X										
Hepatitis B Virus antibody (if HBsAg positive) [h]	X										
HCV RNA (if HCV positive) [h]	X										
CBC with Differential [i]	X	X				X		X	X	X	
Serum Chemistries [i]	X	X				X		X	X	X	
Coagulation [i]	X	X				X		X	X	X	
TSH and Free T4 [i]	X					X		X [j]		X	

Assessments	Screening	Treatment Period								Follow-up	
		Cycle 1				Cycle 2[a]		Cycles 3~	End of Treatment	Safety Follow-up	
Cycle Day	-28 to -1	1	2	3	8	1	8	1		30 days from last dose	90 days from last dose [b]
Visit Window (Days) [c]	0	0	0	0	0	+ 1	+ 1	± 3 [s]	+ 7	+ 3	± 7
Pregnancy Test [i, k]	X	X				X		X	X		
Testosterone (mCRPC only)	X										
PSA (mCRPC only) [l]	X	Every 8 weeks (± 1 week) from C1D1 until iCPD									
Tumor Marker [m]	Per standard of care or as clinically indicated										
Whole blood - Immune Cell Subsets (flow cytometry) [n]		X			X	X		X	X		
Serum for Circulating Soluble Factors and Cytokines/Chemokines and Oncomarker		See [Table 3] for Sample Collection Schedule									
Serum for Pharmacokinetics		See [Table 3] for Sample Collection Schedule									
Receptor Occupancy		See [Table 3] for Sample Collection Schedule									
Antidrug Antibodies (immunogenicity)		See [Table 3] for Sample Collection Schedule									
Optional Whole Blood Sample (banked for Pharmacogenomics analysis)		X									
Urine Collection											
Urinalysis [i]	X	X				X		X	X		
Tumor Tissue Collection											
Optional Archival Tumor Sample [o]	X										
Radiographic Imaging											
Tumor Imaging [p]	X	Every 8 weeks (± 1 week) from C1D1 until iCPD									
Electrocardiograms											
12-lead ECG [q]	X	See [Table 3] for ECG Schedule									
Study Drug Administration											
ASP1948 (60-minute Infusion -5 to +20 minutes) [r]		X				X		X			

C: cycle; C1D1: Cycle 1 Day 1; CBC: complete blood count; CT: computed tomography; d: day; DLT: dose limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRFs: electronic case report forms; FFPE: formalin-fixed, paraffin-embedded; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C

virus; iCPD: immune confirmed progressive disease by iRECIST; IP: investigational product; mCRPC: metastatic castration resistant prostate cancer; MRI: magnetic resonance imaging; PSA: prostate specific antigen; T4: thyroxine; TSH: thyroid stimulating hormone
Footnotes on next page

a. For C2D8, if in the investigator's opinion the subject is clinically stable, a telephone contact to the subject to assess adverse events and concomitant medication use can be performed in lieu of an onsite visit. In these instances, the subject will not be required to perform vital signs.

b. The 90-day safety follow-up visit is optional for subjects who discontinue due to progressive disease or initiate new anticancer treatment after the last dose of IP.

c. The visit window for Day 1 of each cycle is calculated from the actual Day 1 of last cycle. The visit window for Day 8 of each cycle is calculated from the actual Day 1 of the cycle. End of Treatment visit will occur within 7 days of last dose or decision by the investigators to discontinue the subject from treatment.

d. Obtain vital signs within 15 minutes prior to start of ASP1948 dosing, every 15 minutes (-5 to + 10 minutes window) during ASP1948 dosing, at the end of ASP1948 dosing (-5 to + 10 minutes window) and 30 minutes (± 10 minutes) after completion of ASP1948 dosing.

e. As a result of auscultation, a chest X-ray examination, sialylated carbohydrate antigen (KL-6) and transcutaneous arterial oxygen saturation (SpO_2) may be performed if clinically indicated.

f. Includes any prior antitumor medications related to the primary cancer and all anticancer treatment that is taken within 28 days prior to IP administration.

g. AEs will be collected from the time of informed consent through 30 days following the last dose of IP or until initiation of a new anticancer treatment or the subject is determined to be a screen failure, whichever comes first. SAEs (regardless of causality) will be collected from the time of informed consent through 90 days following the last dose of IP or until initiation of a new anticancer treatment or the subject is determined to be a screen failure, whichever comes first.

h. HBsAg, Immunoglobin M antibody to Hepatitis B core antigen (IgM anti-HBc), total antibody to Hepatitis B core antigen (total anti-HBc) (confirmed by HBV DNA using the polymerase chain reaction) will be assessed during HBV testing. HBc antibodies will be tested, if HBsAg is positive. HCV antibody will be tested and HCV RNA will be detected, if HCV antibody is positive.

i. Screening safety laboratory tests should be done within 7 days prior to the initiation of IP. After Cycle 1, safety laboratory tests on Day 1 of each cycle can be performed up to 72 hours prior to scheduled treatment point.

j. TSH and free T4 to be measured on Day 1 of every other cycle after Cycle 2 (i.e., C4, C6, C8, etc.) and at the 30-day safety follow-up visit.

k. Urine or serum pregnancy test will be performed in women of childbearing potential. Testing at treatment visits must occur prior to IP administration.

l. PSA (mCRPC only) will be collected within 14 days prior to C1D1 and while on study approximately every 8 weeks (i.e., C5, C9, C13, etc.).

m. Information regarding tumor marker (e.g., CA-125) tests done as a standard of care may be recorded in the eCRFs, if available.

n. Samples should be collected predose at C1D1, C2D1, C3D1, C5D1. Samples are also collected on C1D8 and at the End of Treatment visit.

o. Archival tumor specimen is optional. A minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 10 FFPE unstained serial slides are required. If ≥ 10 slides cannot be provided, the sponsor should be contacted for further guidance.

p. To ensure comparability, the same technique (CT/MRI) used at Screening should be utilized throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the subject's disease. Scans performed prior to informed consent as standard of care are acceptable as screening scans, if done within 28 days prior to C1D1.

q. Prior to performing ECG, subjects should rest in supine position (or semirecumbent, if supine is not tolerated) for 10 minutes. When ECGs are performed in triplicates, it should be recorded with 2 minutes apart per time point. Single ECG will be done at Screening and End of Treatment. All ECGs will be submitted for central read.

r. ASP1948 is administered on Day 1 of each 14-day cycle. In principle, subjects must be hospitalized from C1D1 (first dose of ASP1948) to C2D14. If it is deemed possible to follow a subject on an outpatient basis based on his/her physical condition, etc. during the DLT observation period, the investigator must ensure his/her safety under outpatient management by performing the tests considered clinically necessary before discharge (observation and evaluation of general condition, blood tests, etc.). For the next 3 doses (third, fourth and fifth infusions), subjects should remain at the site facility for at least 2 hours after completion of ASP1948 administration. The subject should be instructed to notify site personnel if the subject develops any AEs during this time period.

s. The visit window of Cycle 3 Day 1 is "+3".

Table 2 Schedule of Assessments for Dose level C

Assessments	Screening	Treatment Period											Follow -up	
		Cycle 1					Cycle 2			Cycles 3 -		End of Treatment	Safety Follow - up	
Cycle Day	-28 to -1	1	2	3	8	15	1	8 [a]	15	1	15 [a]		30 days from last dose	90 days from last dose [b]
Visit Window (Days) [c]		0	0	0	0	0	+ 2	± 2	± 2	± 2	± 2	+7	+3	± 7
General Study Procedures														
Informed Consent	X													
Verify Inclusion/Exclusion	X	X												
Medical History/Disease History/Demographics	X													
Height	X													
Weight	X	X					X			X		X		
Vital Signs	X	X [d]			X	X	X [d]	X	X	X [d]	X	X	X	X
Physical Examination (including auscultation) [e]	X	X				X	X			X		X		
ECOG Performance Status	X	X					X			X		X	X	
Prior/Concomitant Medications [f]	Every visit													
AE Assessment [g]	Every visit													X
Blood Collection														
Hepatitis B and C Testing [h]	X													
Hepatitis B virus antibody (if HBsAg positive) [h]	X													
HCV RNA (if HCV positive) [h]	X													
CBC with Differential [i]	X	X				X	X		X	X		X	X	
Serum Chemistries [i]	X	X				X	X		X	X		X	X	
Coagulation [i]	X	X				X	X		X	X		X	X	
TSH and Free T4 [i]	X						X			X [j]			X	
Pregnancy Test [i, k]	X	X					X			X		X		
Testosterone (mCRPC only)	X													
PSA (mCRPC only) [l]	X	Every 9 weeks (± 1 week) from C1D1 until iCPD												

Assessments	Screening	Treatment Period											Follow -up	
		Cycle 1					Cycle 2			Cycles 3 -		End of Treatment	Safety Follow - up	
Cycle Day	-28 to -1	1	2	3	8	15	1	8 [a]	15	1	15 [a]		30 days from last dose	90 days from last dose [b]
Visit Window (Days) [c]		0	0	0	0	0	+ 2	± 2	± 2	± 2	± 2	+7	+3	± 7
Tumor Marker [m]	Per standard of care or as clinically indicated													
Whole blood - Immune Cell Subsets (flow cytometry) [n]		X			X		X			X		X		
Serum for Circulating Soluble Factors and Cytokines/Chemokines and Oncomarker		See [Table 4] below for Sample Collection Schedule												
Serum for Pharmacokinetics		See [Table 4] below for Sample Collection Schedule												
Receptor Occupancy		See [Table 4] below for Sample Collection Schedule												
Anti-drug Antibodies (Immunogenicity)		See [Table 4] below for Sample Collection Schedule												
Optional whole blood sample (banked for Pharmacogenomics analysis)		X												
Urine Collection														
Urinalysis [i]	X	X				X	X		X	X		X		
Tumor Tissue Collection														
Optional Tumor Samples [o]	X								X					
Radiographic Imaging														
Tumor Imaging [p]	X	Every 9 weeks (± 1 week) from C1D1 until iCPD												
Electrocardiograms														
12-lead ECG [q]	X	See [Table 4] below for ECG schedule												
Study Treatment Administration														
ASP1948 (60 minute Infusion -5 to +20 minutes) [r]		X					X			X				

C: cycle; C1D1: Cycle 1 Day 1; CBC: complete blood count; CT: computed tomography; d: day; DLT: dose limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; eCRFs: electronic case report forms; FFPE: formalin fixed, paraffin embedded; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; iCPD: immune confirmed progressive disease by iRECIST; IP: investigational product; mCRPC: metastatic castration resistant prostate cancer; MRI: magnetic resonance imaging; PSA: prostate specific antigen; T4: thyroxine; TSH: thyroid stimulating hormone

a. For visits where the only procedures required are vital sign assessment, adverse event review and concomitant medication review, if in the investigator's opinion the subject is clinically stable, a telephone contact to the subject to assess adverse events and concomitant medication use can be performed in lieu of an onsite visit. In these instances, assessment of the subject's vital signs will not be required.

b. The 90-day safety follow-up visit is optional for subjects who discontinue due to progressive disease or initiate new anticancer treatment after the last dose of IP.

c. The visit window for Day 1 of each cycle is calculated from the actual Day 1 of last cycle. The visit window for Day 8 and 15 of each cycle is calculated from the actual Day1 of the cycle. End of Treatment visit will occur within 7 days of last dose or decision by the investigators to discontinue the subject from treatment.

d. Obtain vital signs within 15 minutes prior to start of ASP1948 dosing, every 15 minutes (-5 to + 10 minutes window) during ASP1948 dosing, at the end of ASP1948 dosing (-5 to + 10 minutes window) and 30 minutes (± 10 minutes) after completion of ASP1948 dosing.

e. As a result of auscultation, a chest X-ray examination, sialylated carbohydrate antigen (KL-6) and transcutaneous arterial oxygen saturation (SpO_2) may be performed if clinically indicated.

f. Includes any prior antitumor medications related to the primary cancer and all anticancer treatment that is taken within 28 days prior to IP administration.

g. AEs will be collected from the time of informed consent through 30 days following the last dose of IP or until initiation of a new anticancer treatment or the subject is determined to be a screen failure, whichever comes first. SAEs (regardless of causality) will be collected from the time of informed consent through 90 days following the last dose of IP or until initiation of a new anticancer treatment or the subject is determined to be a screen failure, whichever comes first.

h. HBsAg, Immunoglobin M antibody to Hepatitis B core antigen (IgM anti-HBc), total antibody to Hepatitis B core antigen (total anti-HBc) (confirmed by HBV DNA using the polymerase chain reaction) will be assessed during HBV testing. HBc antibodies will be tested, if HBsAg is positive. HCV antibody will be tested and HCV RNA will be detected, if HCV antibody is positive.

i. Screening safety laboratory tests should be done within 7 days prior to the initiation of IP. After Cycle 1, safety laboratory tests on Day 1 of each cycle can be performed up to 72 hours prior to scheduled treatment point.

j. TSH and free T4 to be measured every other cycle after Cycle 2 (i.e., C4, C6, C8, etc.) and at the 30-day safety follow-up visit.

k. Urine or serum pregnancy test will be performed in women of childbearing potential. Testing at treatment visits must occur prior to IP administration.

l. PSA (mCRPC only) will be collected within 14 days prior to C1D1 and approximately every 9 weeks while on study.

m. Information regarding tumor marker (e.g., CA-125) tests done as a standard of care may be recorded in the eCRFs, if available.

n. Samples should be collected predose on C1D1, C2D1, C3D1, C5D1. Samples should also be collected at C1D8 and End of Treatment visits.

o. Archival tumor specimen for Screening period and on-treatment tumor specimen (except for subjects with mCRPC who do not have measurable disease) on C2D15 visit (± 7 days) are optional. On-treatment tumor specimen is to be obtained from a lesion that will be classified as one of the non-target lesions. A minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 10 FFPE unstained serial slides are required. If ≥ 10 slides cannot be provided, the sponsor should be contacted for further guidance.

p. To ensure comparability, the same technique (CT/MRI) used at Screening should be utilized throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the subject's disease. Scans performed prior to informed consent as standard of care are acceptable as screening scans, if done within 28 days prior to C1D1.

q. Prior to performing ECG, subjects should rest in supine position (or semirecumbent, if supine is not tolerated) for 10 minutes. When ECGs are performed in triplicates, it should be recorded with 2 minutes apart per time point. Single ECG will be done at Screening and End of Treatment. All ECGs will be submitted for central read.

r. ASP1948 is administered on Day 1 of each 21-day cycle. In principle, subjects must be hospitalized from C1D1 (first dose of ASP1948) to C1D21. If it is deemed possible to follow a subject on an outpatient basis based on his/her physical condition, etc. during the DLT observation period, the investigator must ensure his/her safety under outpatient management by performing the tests considered clinically necessary before discharge (observation and evaluation of general condition, blood tests, etc.). For the next 3 doses (second, third and fourth infusions), subjects should remain at the site facility for at least 2 hours after completion of ASP1948 administration. The subject should be instructed to notify site personnel if the subject develops any AEs during this time period.

Table 3 Pharmacokinetic, Circulating Soluble Factors, Immunogenicity, Electrocardiogram and Receptor Occupancy Sampling Schedule for Dose level A and Dose level B

Study Day		Time (Relative to Dosing in Each Cycle) [a]	ASP1948 Pharmacokinetics	Circulating Soluble Factors	ASP1948 Immunogenicity	ECG (Triplicate)	ASP1948 Receptor Occupancy
Cycle 1	Day 1	Predose (0 hour) [b]	X	X	X	X	X
		End of dosing [c]	X			X	X
		4 hours after the start of dosing [d]	X			X	
	Day 2	24 hours after the start of dosing [e]	X	X			X
	Day 3	48 hours after the start of dosing [e]	X	X			
	Day 8	168 hours after the start of dosing [e]	X	X			X
Cycle 2	Day 1	Predose (336 hours after start of C1D1 dosing) [b]	X	X	X		X
		End of dosing [c]	X			X	X
Cycles 4 & 7	Day 1	Predose (0 hour) [b]	X	X	X	X	X
		End of dosing [c]	X			X	X
Cycle 10	Day 1	Predose (0 hour) [b]	X	X	X	X	X
		End of dosing [c]	X			X	X
Cycles 16 & 22	Day 1	Predose (0 hour) [b]	X	X	X		
End of Treatment			X	X		X (Not triplicate)	
30-Day Safety Follow-up			X		X		
90-Day Safety Follow-up			X		X		

C1D1: Cycle 1 Day 1; ECG: electrocardiogram

a. Blood samples should be collected after collection of ECG. Blood and ECG samples should be within 30 minutes of each other.

b. Predose window is within 60 minutes prior to dosing.

c. Within 20 minutes after the end of the dosing

d. Window: ± 10 minutes

e. Window: ± 60 minutes

Table 4 Pharmacokinetic, Circulating Soluble Factors, Immunogenicity, Electrocardiogram and Receptor Occupancy Sampling Schedule for Dose level C

Study Day		Time (Relative to Dosing in Each Cycle) [a]	ASP1948 Pharmacokinetics	Circulating Soluble Factors	ASP1948 Immunogenicity	ECG (Triplicate)	ASP1948 Receptor Occupancy
Cycle 1	Day 1	Predose (0 hour) [b]	X	X	X	X	X
		End of dosing [c]	X			X	X
		4 hours after the start of dosing [d]	X			X	
	Day 2	24 hours after the start of dosing [e]	X	X			X
	Day 3	48 hours after the start of dosing [e]	X	X			
	Day 8	168 hours after the start of dosing [e]	X	X			X
	Day 15	336 hours after the start of dosing [e]	X	X			X
Cycle 2	Day 1	Predose (504 hours after start of C1D1 dosing) [b]	X	X	X		X
		End of dosing [c]	X			X	X
Cycles 4 & 7	Day 1	Predose (0 hour) [b]	X	X	X	X	X
		End of dosing [c]	X			X	X
Cycle 10	Day 1	Predose (0 hour) [b]	X	X	X		
Cycles 15	Day 1	Predose (0 hour) [b]	X	X	X		
End of Treatment			X	X		X (Not triplicate)	
30-Day Safety Follow-up			X		X		
90-Day Safety Follow-up			X		X		

C1D1: Cycle 1 Day 1; ECG: electrocardiogram

a. Blood samples should be collected after collection of ECG. Blood and ECG samples should be within 30 minutes of each other.

b. Predose window is within 60 minutes prior to dosing.

c. Within 20 minutes after the end of the dosing

d. Window: ± 10 minutes

e. Window: ± 60 minutes

2 INTRODUCTION

2.1 Background

Cancer is among the leading causes of death worldwide, with an estimated 18.1 million new cases and approximately 9.5 million deaths worldwide in 2018 [National Cancer Institute, 2020]. New therapeutic strategies for the treatment of cancer harness the body's own immune system to mount an antitumor response. Endogenous immune responses are frequently unable to inhibit tumor growth. This deficiency appears to be due to the immunosuppressive nature of the tumor microenvironment (TME). Tumor-infiltrating lymphocytes become 'exhausted' or suppressed in the context of multiple signals in the TME resulting in significantly impaired proliferative capacity and effector function [Lanitis et al, 2017].

T cell responses are controlled by various receptor/ligand interactions, and inhibitory signals provided by the TME are excellent drug targets for 'reawakening' the immune response to the tumor [Pardoll, 2012]. Antibody blockade of T cell inhibitory receptors such as programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) or cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) have exhibited striking antitumor activity in some cancer patients [Borghaei et al, 2015; Garon et al, 2015; Robert et al, 2015; Brahmer et al, 2010]. These successes have generated increased interest in the identification of additional T cell receptor/ligand pairs that may regulate T cell function in the TME. Drugs targeting such molecules may provide opportunities for enhanced efficacy in patients who do not adequately respond to currently approved checkpoint inhibitor (CPI) therapies.

Neuropilin-1 (NRP1) is a multifunctional single-pass transmembrane protein and functions as a homodimer or as a coreceptor of vascular endothelial growth factor (VEGF) receptors for VEGF ligands and Plexin for semaphorin (SEMA) ligands, triggering multiple signaling pathways depending on the cellular context [Jung et al, 2020]. NRP1 has been shown to play a regulatory role in the immune system. Overexpression of NRP1 on the surface of dendritic cells and Tregs has been demonstrated to play a role in promoting tumor development. Within the TME, NRP1 expression is required for Treg stability and function but does not impact Tregs outside the inflammatory environment of tumors [Delgoffe et al, 2013]. Intratumoral NRP1-deleted Tregs produce IFN-γ and promote fragility of neighboring Tregs, boosting antitumor immunity and tumor clearance, demonstrated to be a requirement for response to anti-PD-1 therapy [Overacre-Delgoffe et al, 2017]. NRP1 is also expressed on tumor associated macrophages (TAMs) and plays a crucial role for their migration to the hypoxic microenvironment of the tumor. Deletions in the NRP1 gene in macrophages facilitate the entry of TAMs into the area of normoxic tumors, resulting in abrogating their protumoral functions [Casazza et al, 2013]. In addition, it is known that NRP1 can form complexes directly with several angiogenesis factors (e.g., VEGF and its receptors) to enhance tumor angiogenesis [Hu & Jiang, 2016].

ASP1948, also known as PTZ-329, is a high affinity fully human anti-NRP1 immunoglobulin (Ig)G4 antibody with the S228P hinge modification to ablate IgG4 arm exchange. ASP1948

bound to NRP1 and blocked ligand interaction. In the MC38 syngeneic mouse model, mPTZ-329 dose-related changes were observed in the antitumor efficacy and peripheral immune cell phenotypes such as a decrease of Helios and FoxP3 expression in Tregs, as well as a decrease in their proliferation. In the CT26 syngeneic mouse model, mPTZ-329 displayed antitumor efficacy greater than that of an anti-PD-1 antibody. The combination of mPTZ-329 with the anti-PD-1 antibody resulted in increased antitumor efficacy over that of either treatment alone. In addition, the pharmacological properties of ASP1948 to inhibit angiogenesis was shown in an in vitro study. ASP1948 has a potential to inhibit growth factors-induced angiogenesis tube formation in a HUVEC and NHDF coculture system. The nonclinical package suggests that ASP1948 may have activity in advanced solid tumors.

ASP1948 is expressed and purified from Chinese hamster ovary (CHO) cells. ASP1948 has a high affinity for human, cynomolgus monkey, rat and mouse recombinant NRP1.

2.1.1 Nonclinical and Clinical Data

2.1.1.1 Nonclinical Data

Several nonclinical in vitro pharmacology studies of ASP1948 (also known as PTZ-329) have been conducted. Antitumor efficacy of ASP1948 was demonstrated in 2 syngeneic mouse colon tumor models using mPTZ-329 (a chimeric of ASP1948 and mouse IgG2a scaffold with the N297A mutation to abolish antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity effector functions).

2.1.1.1.1 Pharmacology

ASP1948 blocked binding of human NRP1 to ligands SEMA3A and VEGFA with potent 50% inhibitory concentration values of 1.7 nmol/L and 3.6 nmol/L, respectively.

A pharmacologic dose-response study of mPTZ-329, a chimeric version of ASP1948 consisting of a mouse IgG2a scaffold with the N297A mutation to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effector functions, conducted in the MC38 syngeneic mouse tumor model demonstrated that efficacy occurred with maximum receptor occupancy (RO) when circulating levels of mPTZ-329 were maintained above approximately 100 µg/mL. Dose-dependent changes were observed in peripheral immune cell phenotypes such as a decrease of Helios and FoxP3 expression in Tregs, as well as a decrease in their proliferation. Importantly, these effects were not observed in the group treated with a PD-1 pathway inhibitor alone. In the CT26 syngeneic mouse model, the antitumor efficacy of mPTZ-329 in combination with an anti-PD-1 antibody was shown. As a single agent, mPTZ-329 displayed antitumor efficacy greater than that of the anti-PD-1 antibody. The combination of mPTZ-329 with the anti-PD-1 antibody resulted in increased antitumor efficacy over that of either treatment alone. Antitumor efficacy correlated with full receptor occupancy of NRP1, which was achieved in the mPTZ-329 and mPTZ-329/anti-PD-1 antibody treated groups. mPTZ-329 as a single agent or in combination with an anti-PD-1 antibody resulted in significant decreases in the expression levels of NRP1 and the transcription factor Helios on splenic Tregs, as well as decreases in Treg proliferation. Restimulation of cluster of differentiation (CD) 8+ T cells isolated from tumors treated in

vivo with the combination of mPTZ-329 and anti-PD-1 antibody had a significantly higher frequency of cells producing IFNγ and tumor necrosis factor (TNF), as well as a significantly higher frequency of CD8+ T cells producing both cytokines simultaneously.

In a human umbilical vein endothelial cell and normal human dermal fibroblast coculture system, ASP1948 inhibited angiogenesis tube formation induced by growth factors including VEGF.

Safety pharmacology assessments evaluating the effect of ASP1948 on the central nervous, cardiovascular and respiratory system were included in the 4-week (5-dose) repeat-dose toxicity study in cynomolgus monkeys. No abnormal findings were noted in any safety pharmacology parameter up to 200 mg/kg.

Refer to the current IB for additional details.

2.1.1.1.2 Pharmacokinetics

The pharmacokinetics and toxicokinetics of ASP1948 were characterized in rats and cynomolgus monkeys in single- and repeat-dose studies. The pharmacokinetics of ASP1948 is characterized by target-mediated drug disposition (TMDD), with nonlinear behavior after a single dose of 3 to 30 mg/kg in both rats and cynomolgus monkeys, and approximately linear pharmacokinetic behavior after repeated doses of 50 to 500 mg/kg in rats and 20 to 200 mg/kg in cynomolgus monkeys. No apparent gender differences were observed in exposure in both rats and cynomolgus monkeys. In the pharmacokinetic studies, antidrug (ASP1948) antibodies (ADAs) were observed in rats treated at 3 to 30 mg/kg and in monkeys treated at 3 to 10 mg/kg. No animals were found positive for ADAs after ASP1948 administration (50 to 500 mg/kg in rat and 20 to 200 mg/kg in cynomolgus monkeys) in the Good Laboratory Practice (GLP) toxicity studies. A modeling and simulation study was conducted to support dose selection for the first-in-human (FIH) study of ASP1948. The model predicted that when dosing every 2 weeks (Q2W), a 70-mg dose of ASP1948 will transiently saturate TMDD (< 1 day) and a 1200-mg dose of ASP1948 will saturate TMDD throughout the dosing interval.

No conventional metabolism and excretion studies were conducted with ASP1948. Such studies are not considered relevant for a monoclonal antibody product since catabolic degradation to small peptide and amino acids is the expected pathway of metabolism and excretion of intact ASP1948 in urine is not expected due to its molecular size [Keizer et al, 2010].

Refer to the current IB for additional details.

2.1.1.1.3 Toxicology

Toxicology studies consisted of 2 in vivo studies and 2 in vitro studies; (1) a 4-week (5-dose) repeated intravenous dose toxicity study in rats, (2) a 4-week (5-dose) repeated intravenous dose toxicity study in cynomolgus monkeys, (3) an in vitro tissue crossreactivity study in human and cynomolgus monkey tissues and (4) an in vitro cytokine release and proliferation assessment in human peripheral blood mononuclear cells (PBMCs). Intravenous

administration of ASP1948 to rats at dose levels of 50, 150 or 500 mg/kg weekly for 4 weeks (total of 5 doses) resulted in no drug related adverse effects or toxicologically relevant findings. Therefore, the no observed adverse effect level (NOAEL) was considered to be 500 mg/kg/dose (C_{max} 13500 µg/mL and AUC_{168h} 1178400 µg·h/mL, gender combined) for rats.

In the repeated dose toxicity study in cynomolgus monkeys, intravenous administration of ASP1948 weekly for 4 weeks (total of 5 doses) at dose levels of 20, 60 or 200 mg/kg showed no adverse findings in any parameters examined. ASP1948 was well tolerated at doses up to 200 mg/kg, and based on these results, the NOAEL was considered to be 200 mg/kg/dose (C_{max} 7320 µg/mL and AUC_{168h} 809000 µg·h/mL, gender combined) for cynomolgus monkeys.

The staining observed with ASP1948 in cynomolgus monkey and human tissues in the tissue crossreactivity study was cytoplasmic in nature, with the exception of the neuropil staining observed in a single monkey brain sample.

A non-Good Laboratory Practice in vitro cytokine release and proliferation study in human PBMCs was performed using 2 assay formats; 1 was wet-coated format and the other a soluble format. For the wet-coated format, ASP1948 was immobilized to an assay plate, while in the soluble format, PBMCs were incubated with ASP1948 in solution. An increased release of interleukin (IL)-6 at 30 µg/mL or more and the increases of IL-1ß, IL-8, TNF alpha and granulocyte colony stimulating factor at 300 µg/mL were noted in the soluble format assay, while no increase of cytokines were observed in the wet-coated assay. In vitro incubation with ASP1948 did not induce the proliferation of human PBMCs.

Based on the currently available safety data, it was concluded that there were no identified toxicological findings that would preclude initiation of a phase 1 study in ASP1948. Cytokine release was noted in vitro, the clinical impact of which is unknown. Monitoring of appropriate parameters (e.g., cytokines and signs) in the clinical study should be considered.

Refer to the current IB for additional details.

2.1.1.2 Clinical Data

2.1.1.2.1 Phase 1 Results (1948-CL-0101)

Study 1948-CL-0101 is a first in human, open-label, dose escalation and expansion study investigating the tolerability, safety, pharmacokinetics and recommended phase 2 dose (RP2D) in patients with locally advanced (unresectable) or metastatic solid tumors, is currently ongoing, and safety data from 157 patients with advanced solid tumors exposed to ASP1948 are available.

As of data cut-off of Apr 26, 2021, patients received ASP1948 as monotherapy or in combination with nivolumab or pembrolizumab. Monotherapy ASP1948 was administered at 6 dose levels: 70 mg (n = 3), 200 mg (n = 3), 700 mg (n = 6), 1200 mg (n = 4) and 2000 mg (n = 67) Q2W and 3000 mg (n = 8) every 3 weeks (Q3W). Patients receiving combination therapy with nivolumab were administered ASP1948 Q2W at a dose of 1200 mg

(n = 4) or 2000 mg (n = 18) with a fixed dose of nivolumab (240 mg Q2W). Patients receiving combination therapy with pembrolizumab were administered ASP1948 2000 mg Q2W with pembrolizumab 400 mg every 6 weeks (n = 7) or ASP1948 3000 mg Q3W with pembrolizumab 200 mg Q3W (n = 37).

Preliminary pharmacokinetic data from Study 1948-CL-0101 monotherapy escalation cohorts revealed that ASP1948 Cmax and AUC14-day appeared to be over dose-proportional between the 70 to 700 mg dose levels, and approximately dose-proportional at dose levels > 700 mg. The mean t1/2 of ASP1948 at the 2000 mg dose level was 7.9 days.

Immunogenicity data from 128 patients enrolled in monotherapy and combination therapy cohorts in Study 1948-CL-0101 revealed that 2 (2.0%) patients had de novo anti-ASP1948 antibodies present.

Preliminary response data from Study 1948-CL-0101 for the 70 patients treated with ASP1948 monotherapy included in the efficacy analysis showed that 30 (42.9%) patients had stable disease and 39 (55.7%) patients had progressive disease (PD) as their best overall response (BOR) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. No patients in the monotherapy cohort had a confirmed complete response (CR) or partial response (PR) using RECIST 1.1 or modified RECIST 1.1 for immune-based therapeutics (iRECIST). For the 18 patients treated with ASP1948 combination therapy with nivolumab included in the analysis, 1 (5.6%) patient had confirmed PR at the 1200 mg dose level, 8 (44.4%) patients had stable disease and 8 (44.4%) patients had PD as their BOR using RECIST 1.1. No patients in the nivolumab combination therapy cohort had a confirmed CR using RECIST 1.1 or iRECIST. For the 12 patients treated with ASP1948 combination therapy with pembrolizumab included in the analysis, 5 (41.7%) patients had stable disease and 6 (50.0%) patients had PD as their BOR using RECIST 1.1. No patients in the pembrolizumab combination therapy cohort had a confirmed CR or PR using RECIST 1.1 or iRECIST.

84 (92.3%) of 91 patients dosed with ASP1948 monotherapy experienced treatment-emergent adverse events (TEAEs), 41 (45.1%) patients experienced at least 1 TEAE considered to be related to ASP1948 by the investigator and 35 (38.5%) patients experienced TEAEs that were Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3. A total of 26 (28.6%) patients experienced 1 or more serious TEAEs. Overall, 7 (7.7%) patients experienced TEAEs that led to death: non-small cell lung cancer (2 patients) and cardiac arrest, melena, hepatic failure, clostridium difficile colitis, sepsis, lactic acidosis, malignant neoplasm progression and tumor hemorrhage (1 patient each). The events of hepatic failure, lactic acidosis and tumor hemorrhage were considered related to ASP1948 by the investigator. Immune-related AEs (irAEs) were experienced by 6 (6.6%) patients, all at the 2000-mg dose level, and infusion-related reactions (IRRs) were experienced by 3 (3.3%) patients, 1 at the 700-mg dose level and 2 at the 2000-mg dose level. There were 2 patients who experienced a total of 3 dose-limiting toxicity events at the 2000-mg dose level (hepatic enzyme increased, hepatic failure and tumor hemorrhage).

For patients dosed with ASP1948 in combination with nivolumab in Study 1948-CL-0101, 22 (100.0%) of 22 patients experienced TEAEs, 13 (59.1%) patients experienced at least 1 TEAE considered to be related to ASP1948 by the investigator and 13 (59.1%) patients experienced TEAEs that were CTCAE grade ≥ 3. A total of 8 (36.4%) patients experienced 1 or more serious TEAEs. Two (9.1%) patients experienced TEAEs that led to death: COVID-19 and malignant neoplasm progression. Neither event was considered related to ASP1948 by the investigator. irAEs were experienced by 3 (13.6%) patients, 1 at the 1200-mg dose level and 2 at the 2000-mg dose level, and IRRs were experienced by 1 (4.5%) patient at the 2000-mg dose level. There were no dose-limiting toxicities up to the 2000-mg dose level.

For patients dosed with ASP1948 in combination with pembrolizumab in Study 1948-CL-0101, 32 (72.7%) of 44 patients experienced TEAEs, 20 (45.5%) patients experienced at least 1 TEAE considered to be related to ASP1948 by the investigator and 15 (34.1%) patients experienced TEAEs that were CTCAE grade ≥ 3. A total of 14 (31.8%) patients experienced 1 or more serious TEAEs. Two (4.5%) patients experienced TEAEs that led to death: small intestinal obstruction and malignant neoplasm progression. Neither event was considered related to ASP1948 by the investigator. irAEs were experienced by 6 (13.6%) patients, 1 at the 2000-mg dose level and 5 at the 3000-mg dose level, and IRRs were experienced by 4 (9.1%) patients, all at the 3000-mg dose level. One patient experienced a dose-limiting toxicity event at the 3000-mg dose level (pruritus).

Refer to the current IB for additional details.

2.1.1.2.2 Phase 1 Results (1948-CL-0102)

As of data cut-off of Apr 26, 2021, safety data from 9 patients with advanced solid tumors exposed to ASP1948 are available. Patients received ASP1948 monotherapy at 1200 mg (n = 3) or 2000 mg (n = 3) Q2W or 3000 mg (n = 3) Q3W.

Preliminary pharmacokinetic data from Study 1948-CL-0102 monotherapy escalation cohorts revealed that ASP1948 Cmax and AUC14-day increased dose dependently after the first dose.

Preliminary response data in Study 1948-CL-0102 (data cutoff 26 Apr 2021) for the 9 patients treated with ASP1948 monotherapy showed that 1 (11.1%) patient had confirmed PR at the 1200-mg dose level, 2 (22.2%) patients had stable disease and 6 (66.7%) patients had PD as their BOR using RECIST 1.1. No patients had a confirmed CR using RECIST 1.1 or iRECIST.

8 (88.9%) of 9 patients dosed with ASP1948 monotherapy experienced TEAEs, 7 (77.8%) patients experienced at least 1 TEAE considered to be related to ASP1948 by the investigator and 2 (22.2%) patients experienced TEAEs that were CTCAE grade ≥ 3. Two (22.2%) patients experienced a total of 2 serious TEAEs. One (11.1%) patient experienced a TEAE that led to death (malignant neoplasm progression) which was considered not related to ASP1948 by the investigator. There were no irAEs. IRRs were experienced by 1 (11.1%) patient at the 3000-mg dose level. There were no dose-limiting toxicities up to the 3000-mg dose level.

Refer to the current IB for additional details.

2.1.2 Summary of Key Safety Information for Investigational Product

As of the preparation of this protocol, the safety profile, contraindications and possible warnings and precautions of ASP1948 have not been established. ASP1948 is contraindicated in patients with severe hypersensitivity to any of its components or CHO cell proteins.

Refer to the current IB for additional details.

2.1.2.1 Potential Toxicities

The potential risks described below are based on published literature [see Appendix 12.9 Monitoring of Potential Immune-related Adverse Events, Appendix 12.10 Guidelines for Management of Potential Immune-related Adverse Events, Appendix 12.11 Guidelines for Standard Infusion-related Reactions and Anaphylaxis]. It is not yet known if the immune RO by ASP1948 will result in toxicities similar to those observed with agents targeting other immune receptors.

2.1.2.1.1 Infusion-related Reactions

IRRs are a potential toxicity [see Appendix 12.11 Guidelines for Standard Infusion-related Reactions and Anaphylaxis], although ASP1948 is a fully human IgG4 and is not an immune receptor agonist. The ability to define the clinical risk of cytokine release from the nonclinical data is limited, and cytokine release syndrome (CRS) should be considered a potential risk for any monoclonal antibody [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, 2019].

The majority of IRRs to monoclonal antibodies represent “standard” infusion reactions, and the most common manifestations of these standard infusion reactions include: fever and/or shaking/chills; flushing and/or itching; changes in heart rate and blood pressure; shortness of breath or chest discomfort; pain in back or abdomen; nausea, vomiting and/or diarrhea and skin rash (various types). Fever and muscle pain suggest that the reaction is a standard infusion reaction (as opposed to an allergic reaction discussed below). The exact mechanism causing standard infusion reactions with monoclonal antibodies is unclear, but most reactions appear to arise from cytokine release.

The clinical manifestations of CRS vary greatly and many features resemble infection, with fever being a hallmark. In addition to the symptoms and signs associated with a standard infusion reaction, CRS may also result in neurologic symptoms and signs, including headache, mental status changes, confusion, delirium, word finding difficulty or aphasia, hallucinations, tremor, dysmetria, altered gait or seizures. Renal and hepatic manifestations may include azotemia and elevated transaminases and hyperbilirubinemia, respectively. Coagulation parameters may also be affected, as manifested by elevated D-dimer and

hypofibrinogenemia, with or without bleeding. Severity of CRS also varies greatly. Complications of CRS that may be life threatening include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure and disseminated intravascular coagulation. Findings of macrophage activation syndrome/hemophagocytoic lymphohistiocytosis and tumor lysis syndrome may also be associated with CRS [Lee et al, 2014]. Subjects should be closely monitored for IRRs and CRS and appropriately managed [LaCasce et al, 2019]. Tocilizumab may be considered for the management of CRS.

Although rare, anaphylaxis is a potential risk associated with infusion of monoclonal antibodies. Anaphylaxis caused by intravenously administered medications most often presents with cutaneous, respiratory, cardiovascular or gastrointestinal symptoms that overlap with IRRs; however, fever and muscle pain are not features of anaphylaxis. The signs and symptoms that are highly suggestive of anaphylaxis include: urticaria, repetitive cough, wheeze and throat tightness/change in voice [LaCasce et al, 2019].

2.1.2.1.2 Immune-related Adverse Events

Although not observed in the ASP1948 repeat-dose toxicology study, irAEs represent a potential risk given that they have been observed with other immune CPIs (i.e., CTLA-4 antagonists and PD-1 pathway inhibitors including nivolumab) [see Appendix 12.9 Monitoring of Potential Immune-related Adverse Events, Appendix 12.10 Guidelines for Management of Potential Immune-related Adverse Events]. IrAEs observed with currently approved CPIs include rash, oral mucositis, dry mouth, colitis/diarrhea, hepatitis, pneumonitis and endocrinopathies (hypophysitis, hypothyroidism, hyperthyroidism, adrenal insufficiency and Type 1 diabetes mellitus). Other less frequent irAEs associated with CPIs include: nephritis; pancreatitis; myositis; arthritis; neurologic toxicities (Guillain-Barré syndrome, myasthenia gravis, posterior reversible encephalopathy syndrome, aseptic meningitis, enteric neuropathy, transverse myelitis and autoimmune encephalitis), cardiotoxicity (myocarditis and conduction abnormalities); hematologic toxicity (red cell aplasia, neutropenia, thrombocytopenia, acquired hemophilia A and cryoglobulinemia); and eye inflammation (episcleritis, conjunctivitis, uveitis or orbital inflammation). Early identification of irAEs and prompt initiation of immunosuppression (local or systemic) are important for optimal management of irAEs. Management of irAEs (after interrupting the immune CPI) includes temporary immunosuppression with corticosteroids (starting at Grade 2 events) and in some cases TNF alpha antagonists, myophenolate mofetil or other agents if symptoms do not improve promptly with corticosteroids [Postow et al, 2017].

2.1.2.1.3 Increased Globulin/Increased Total Protein

Nonclinical safety data at high doses of circulating ASP1948 showed nonadverse increases in globulin and decrease in albumin/globulin ratio in monkeys, resulting in no significant sequelae. In addition to this data, rats were also noted to have an increase in total protein. There was no evidence of irreversible histopathological changes in either monkeys or rats and the changes were reversible. Therefore, it is recommended to monitor blood chemistries to evaluate the function of kidneys and other organs due to the potential risks of increased globulin and total protein.

2.2 Study Rationale

ASP1948 is a high affinity fully human anti-NRP1 IgG4 antibody, which binds to NRP1 to block ligand interactions on the surface of Tregs to reverse the suppressive activity of these cells. NRP1 is expressed on Tregs, and this expression identifies a highly-suppressive Treg subset [Prud'homme et al, 2012; Bruder et al, 2004]. Intratumoral Tregs depleted of NRP1 produce IFNγ and promote fragility of neighboring Tregs, boosting antitumor immunity and tumor clearance [Overacre-Delgoffe et al, 2017]. These data suggest that NRP1 is required for Treg lineage stability and function and that targeting NRP1 is an attractive option for the specific inhibition of Tregs in tumors.

ASP1948 as a single agent modulated the immunosuppressive phenotype Tregs and promoted immune mediated reduction of tumor burden, as shown in murine syngeneic tumor models. The antitumor efficacy of ASP1948 was demonstrated using mPTZ-329, a chimeric version of ASP1948. Antitumor efficacy correlated with full RO of NRP1. mPTZ-329 resulted in significant decreases in the expression levels of NRP1 and the transcription factor Helios on splenic Tregs, as well as decreases in Treg proliferation. In a pharmacologic dose-response study of mPTZ-329 in the MC38 colon tumor model, antitumor efficacy occurred when circulating levels of mPTZ-329 were maintained above approximately 100 µg/mL and maximum RO was sustained. Dose-dependent changes were observed in peripheral immune cell phenotypes such as a decrease of Helios and FoxP3 expression in Tregs, as well as a decrease in their proliferation. These data suggest that ASP1948 may have activity in advanced solid tumors.

This first in Japanese study will evaluate ASP1948 as monotherapy (Dose level A: ASP1948, 1200 mg Q2W; and Dose level B: ASP1948, 2000 mg Q2W; and Dose level C: ASP1948, 3000 mg once every 3 weeks [Q3W]). Dose levels will be evaluated in multiple subject cohorts. Subjects will receive ASP1948 as monotherapy every 14 days for Dose level A and Dose level B, or every 21 days for Dose level C. A conservative observation period of 28 days (2 treatment cycles) for Dose level A and Dose level B, or 21 days (1 treatment cycle) for Dose level C will be implemented. For subjects in Dose level A, intra-subject dose escalation is allowed in the judgment of the investigator, in subjects who did not experience a DLT, if Dose level B (ASP1948, 2000 mg) is deemed tolerable at the DESC, so that subjects in Dose level A will be allowed to be administered taking into protecting subject safety consideration.

2.3 Risk Benefit Assessment

ASP1948 is a type of immunotherapy that blocks proteins that prevent cells of the immune system from attacking and destroying cancer cells.

The study population is restricted to Japanese subjects with advanced/metastatic solid tumors who have received, declined or had a contraindication to all therapy with established clinical benefit for their malignancy. Strict adherence to the eligibility criteria is essential to ensure investigators select appropriate subjects for participation in the study.

The potential risk of irAEs and IRRs may be mitigated by closely monitoring subjects' symptoms, signs and clinical laboratory test results to facilitate early identification and management, as per the guidelines in [Appendix 12.9 Monitoring for Potential Immune-related Adverse Event], and in [Appendix 12.11 Guidelines for Standard Infusion-related Reactions and Anaphylaxis]. The management of such toxicities should be based on institutional standard of care and published guidelines, [see Appendix 12.10 Guidelines for Management of Potential Immune-related Adverse Events], as appropriate based on investigator judgment, and on the protocol instructions regarding interruption or discontinuation of investigational product (IP) treatment.

Monoclonal antibodies targeting other immune checkpoints (CTLA-4 antagonists and PD-1 pathway inhibitors) can result in stimulation of the immune system to generate antitumor activity. Immune CPIs target the negative regulators of the immune response rather than the tumor itself; thus these agents are not specific to any type of malignancy. To date, CPIs have shown antitumor activity in various tumor types.

Overall, the risk associated with participation in this clinical study of ASP1948 is considered to be acceptable for this population of Japanese subjects with advanced/metastatic solid tumors who have received, declined or had a contraindication to all therapy with established clinical benefit for their malignancy.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

Table 5 Study Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
• To evaluate the tolerability and safety profile of ASP1948 in Japanese patients with locally advanced (unresectable) or metastatic solid tumors.	• Safety and tolerability as noted by the following: dose limiting toxicities (DLTs), adverse events (AEs), immune-related AEs (irAEs), infusion-related reactions (IRRs), serious adverse events (SAEs), laboratory test results (complete blood count [CBC], serum chemistry, urinalysis, prothrombin time/international normalized ratio [PT/INR], activated partial thromboplastin time [aPTT], thyroid stimulating hormone [TSH] and free thyroxine [free T4]), electrocardiograms (ECGs), vital signs, physical exams and Eastern Cooperative Oncology Group (ECOG) Performance Status.
• To characterize the pharmacokinetic profile of ASP1948 in Japanese patients.	• Pharmacokinetic parameters (AUC_{last}, AUC_{inf} [and %extrap], AUC_{tau}, C_{max}, C_{trough}, t_{max}, $t_{½}$, t_{last}, CL, and V as applicable) of ASP1948.
Secondary	
• To evaluate the antitumor effect of ASP1948.	• Sum of diameters (SOD) for the subjects with at least 1 measurable lesion, which is defined as the sum of all target lesions at a tumor assessment. • Best overall response (BOR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and "immune" Response Evaluation Criteria in Solid Tumors (iRECIST).
Exploratory	
• To evaluate the immunogenicity of ASP1948.	• Immunogenicity of ASP1948 as measured by the frequency of antidrug antibody (ADA)-positive subjects.
• To evaluate target engagement of ASP1948.	• Determination of ASP1948 target engagement by analysis of receptor occupancy on peripheral blood mononuclear cells in subjects treated with ASP1948.
• To evaluate pharmacodynamic activities of ASP1948.	• Pharmacodynamic effects of ASP1948.
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome of ASP1948.	• Exploratory analysis of potential biomarkers of ASP1948 activity.

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

This is a phase 1, open-label study of ASP1948, a fully human monoclonal IgG4 antibody with the S228P hinge stabilization that targets NRP1 expressing intratumoral Tregs affecting their stability/viability and hindering their suppression function. This study consists of 3 dose levels (Dose level A: ASP1948, 1200 mg Q2W; Dose level B: ASP1948, 2000 mg Q2W; and Dose level C: ASP1948, 3000 mg Q3W) and enrollment of subjects into Dose level A will take place first. Dose level B would only be opened if Dose level A is deemed tolerable. Dose level C would only be opened if Dose level B is deemed tolerable. This study will be performed at 1 site in Japan.

4.1.1 Study Periods

The study consists of 2 periods: Screening (up to 28 days) and treatment period (see Figure 1). The DLT observation period is set at the beginning of the treatment period of each dose level. A subject can continue to participate in the study after the end of the DLT observation period until discontinuation criteria are met. After discontinuation of IP, all subjects will complete an End of Treatment visit, along with 30-day and 90-day safety follow-up visits from the last dose of IP. The 90-day safety follow-up visit is optional for subjects who discontinue due to progressive disease (PD) or initiate new anticancer treatment after the last dose of IP.

4.1.2 Definitions of Cycle and Dose Limiting Toxicity Observation Period

A cycle is defined as 14 days (2 weeks) for Dose level A and Dose level B, or 21 days (3 weeks) for Dose level C. Dosing occurs on Day 1 of every cycle. The DLT observation period will be 28 days for Dose level A and Dose level B, or 21 days for Dose level C. Note that the DLT observation period is from Cycle 1 Day 1 to Cycle 2 Day 14 for Dose level A and Dose level B, or from Cycle Day 1 to Cycle 1 Day 21 for Dose level C.

The DLT observation period may be extended if deemed appropriate by the DESC, consisting of sponsor representatives, principal investigator and/or subinvestigators and a statistical advisor.

4.1.3 Tolerability Evaluation Procedures

The tolerability of ASP1948 at 1200 mg Q2W (Dose level A), 2000 mg Q2W (Dose level B) and 3000 mg Q3W (Dose level C) will be assessed during the DLT observation period. Subjects will be enrolled first into Dose level A, and then only if Dose level A is determined to be tolerable, Dose level B would be opened. Dose level C would be opened if Dose level B is determined to be tolerable. In principle, 3 subjects will initially be enrolled at each dose level. Any of the ASP1948 related AEs specified as DLTs as defined in the "DLT Criteria" will be assessed during the DLT observation period. Quantitative assessment of DLTs will be performed according to the criteria referring to the Bayesian Optimal Interval (BOIN) Design [Liu et al, 2015] with the target DLT rate of 0.33 and optimal interval of (0.260,

0.395). Table 6 shows the recommended action in the cases of 3 to 9 evaluable subjects for DLT assessment. The maximum number of subjects at a dose level is 9.

Table 6 Recommended Action from the Number of Subjects for DLT Assessment

	Number of Subjects evaluable for DLT Assessment				
Recommended Action	3	4**	5**	6	9
[Tolerable] If the number of subjects with DLTs is the number given in the right cell or less, the dose can be determined to be tolerable.	0	1	1	1	2
[Stay] If the number of subjects with DLTs is equal to the number given in the right cell, enrollment is continued.	1	-	-	2*	3*
[Not tolerable] If the number of subjects with DLTs is the number given in the right cell or more, the dose is determined to be intolerable.	2	2	2	3	4

DESC: dose escalation and safety committee; DLT: dose limiting toxicity

* In case the number of subjects for DLT assessment is 6 and 9, if the recommended action is Stay, the tolerability of the dose will be assessed comprehensively at the DESC. According to a decision at the DESC, an additional 3 subjects may be enrolled to continue the tolerability assessment in case the number of subjects for DLT assessment is 6.

** In case the number of subjects for DLT assessment is 4 or 5, it is considered exceptional, including, for example, if informed consent is obtained from more than 3 subjects in the process of enrolling the initial 3 subjects. In such a case, these subjects will be included for the initial DLT assessment.

DESC will be held after the end of the DLT observation period for all subjects enrolled in each dose level. The sponsor will comprehensively assess the data (including AEs reported for subjects who are unevaluable for DLT), and discuss the tolerability of the current dose with the principal investigator and/or subinvestigators and statistical advisor at the DESC. Based on the results of the discussion, the sponsor will decide the tolerability of the current dose level. Detailed procedures will be provided in a separately prepared procedure manual.

4.1.4 Dose Limiting Toxicity Criteria

A DLT is defined as any of the following AEs (graded using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03) that the investigator (or sponsor) cannot clearly attribute to a cause other than IP:

- 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 nonhematological AE (excluding asymptomatic changes to amylase, lipase and hypophosphatemia)
- Grade ≥ 2 pneumonitis

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN; Grade ≥ 3) in subjects without liver metastases
- AST or ALT > 8 × ULN in subjects with liver metastases
- AST or ALT > 3 × ULN and total bilirubin (TBL) > 2 × ULN (in subject with Gilbert's syndrome: AST or ALT > 3 x ULN and direct bilirubin > 1.5 x ULN)
- TBL > 3 × ULN (Grade ≥ 3)
- Grade ≥ 2 encephalopathy, meningitis or Grade ≥ 2 motor or sensory neuropathy
- Grade ≥ 2 pulmonary or central nervous system (CNS) hemorrhage
- Grade ≥ 3 hemorrhage
- Any grade arterial thrombotic event (angina, myocardial infarction, transient ischemic attack [TIA], cerebrovascular accident [CVA] and any other arterial thromboembolic event)
- Any grade gastrointestinal perforation
- Any grade wound dehiscence
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- IRR that requires the infusion to be discontinued

Febrile neutropenia, thrombocytopenia accompanied by bleeding that requires any transfusion, and anemia requiring transfusion regardless of grade, may be considered DLTs by the investigator (or sponsor). In addition, in case the second and/or third dose for Dose level A and Dose level B, or the second dose for Dose level C cannot be performed within 7 days after a scheduled visit for drug related toxicities not specified in the above bullet list, this may be also considered DLTs by the investigator (or sponsor).

Subjects who are tolerating IP at a dose level that is being reviewed due to the occurrence of DLTs in another subject will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review by the DESC.

4.1.5 Replacement of Subjects

A subject without a DLT who receives less than the prescribed ASP1948 dose during the DLT observation period, or does not complete the DLT observation period for a reason other than DLT (e.g., consent withdrawal), will not be DLT evaluable and may be replaced.

4.1.6 Intra-subject Dose Escalation (Dose Level A Only)

For subjects in Dose level A, intra-subject dose escalation is allowed in the judgment of the investigator, in subjects who did not experience a DLT, if Dose level B (ASP1948, 2000 mg) is deemed tolerable at the DESC.

4.2 Dose Rationale

ASP1948 will be administered at a dose of 1200 or 2000 mg as an intravenous infusion on Day 1 of every 2-week cycle, or 3000 mg as an intravenous infusion on Day 1 of every 3-week cycle.

In the first in human study of ASP1948 [Study 1948-CL-0101], ASP1948 monotherapy dose escalation cohorts of 70, 200, 700, 1200 and 2000 mg at Q2W were completed without DLTs and a maximum tolerated dose has not been reached at these cohorts.

Based on results from the mouse MC38 syngeneic tumor model, the clinical efficacious dose is estimated to be approximately 1200 mg Q2W or beyond. In this clinical study, ASP1948 1200 mg at Q2W is chosen for Dose level A (i.e. as the initial dose), and 2000 mg at Q2W in Dose level B. Both dose levels have demonstrated good tolerability without DLT in Study 1948-CL-0101.

As of the data cut-off date of 10 July 2019, pharmacokinetic data from initial 19 subjects enrolled in the monotherapy dose escalation cohorts of Study 1948-CL-0101 is available. An exploratory population pharmacokinetic model was developed to characterize pharmacokinetics of ASP1948. The model predicated that the targeted ASP1948 C_{trough} of 100 μg/mL will be reached after 2000 mg Q2W administration. The model also predicated that ASP1948 3000 mg Q3W administration will reach similar C_{trough} levels. This clinical study will evaluate 3000 mg at Q3W in Dose level C.

The estimated ASP1948 exposure at 2000 mg at Q2W and 3000 mg at Q3W in humans is projected to be at least 5-fold lower than that observed in NOAEL in the repeat-dose toxicity studies of rat and monkey.

4.3 End of Study Definition

The study start is defined as the date the first subject signs informed consent. End of the study is defined as the last visit or scheduled procedure shown in Schedule of Assessments (Table 1 and Table 2) for the last subject in the study.

5 STUDY POPULATION

Japanese patients with locally advanced (unresectable) or metastatic solid tumor malignancies who have received all standard therapies (unless the therapy is contraindicated or intolerable) felt to provide clinical benefit in the opinion of the treating investigator for his/her specific tumor type. Potential subjects are allowed to be rescreened.

All screening assessments must be completed and reviewed to confirm the potential subject meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

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

1. Institutional review board (IRB)-approved written informed consent must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is ≥ 20 years of age at the time of signing informed consent.
3. Subject has locally advanced (unresectable) or metastatic solid tumor malignancy (no limit to the number of prior treatment regimens) that is confirmed by available pathology records or current biopsy (if needed) and has received all standard therapies (unless the therapy is contraindicated or intolerable) felt to provide clinical benefit in the opinion of the treating investigator for his/her specific tumor type.
4. Subject has an ECOG Performance Status of 0 or 1.
5. Subject's last dose of prior antineoplastic therapy, including any immunotherapy, was at least 21 days prior to initiation of IP administration. A subject with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutation-positive non-small cell lung cancer (NSCLC) is allowed to remain on EGFR tyrosine kinase inhibitor (TKI) or ALK inhibitor therapy until 4 days prior to initiation of IP administration.
6. Subject has completed any radiotherapy (including stereotactic radiosurgery) at least 14 days prior to initiation of IP administration.
7. Subject with metastatic castration resistant prostate cancer (mCRPC) (positive bone scan and/or soft tissue disease documented by computed tomography [CT]/magnetic resonance imaging [MRI]) meets both of the following:
   - Subject has serum testosterone≤ 50 ng/dL at Screening.
   - Subject has had an orchiectomy or plans to continue androgen deprivation therapy (ADT) for the duration of study treatment.
8. Subject has adequate organ function as indicated by the following laboratory values within 7 days prior to initiation of IP administration. (If a subject has received a recent blood transfusion, the laboratory tests must be obtained ≥ 28 days after any blood transfusion.) Note: Growth factors, colony stimulating factors are not permitted in the screening period.

Parameter	Laboratory Value
Hematological	
ANC	≥ 1500/µL
Platelets	≥ 100,000/µL
Hemoglobin	≥ 9 g/dL
Renal	
Creatinine	Either a) ≤ institutional ULN, or b) eGFR* ≥ 45 mL/min/1.73m^2 if creatinine is > ULN *Using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (2009); online calculator: https://www.kidney.org/professionals/kdoqi/gfr_calculator
Hepatic	
Total bilirubin	Either: a) ≤ 1.5 × ULN, or b) Direct bilirubin ≤ ULN **and** TBL < 3 × ULN (for subjects with Gilbert's syndrome)
AST and ALT	≤ 2.5 × ULN
Coagulation	
INR	Either: a) ≤ 1.5 × ULN for subjects not receiving anticoagulants, or b) within desired therapeutic range for subjects receiving anticoagulants
aPTT	Either: a) ≤ 1.5 × ULN for subjects not receiving anticoagulants, or b) within desired therapeutic range for subjects receiving anticoagulants

ALT: alanine aminotransferase; ANC: absolute neutrophil count; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; INR: international normalized ratio; TBL: total bilirubin;ULN: upper limit of normal

9. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
   - Not a woman of childbearing potential (WOCBP; see [Appendix 12.3 Contraception Requirements])
   - WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent throughout the treatment period and for at least 6 months after the final study treatment administration.
10. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 6 months after the final study treatment administration.
11. Female subject must not donate ova starting at first dose of IP and throughout the study period, and for 6 months after the final study treatment administration.

12. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the treatment period and for at least 6 months after the final study treatment administration.
13. Male subject must not donate sperm during the treatment period and for 6 months after the final study treatment administration.
14. Male subject with a pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 6 months after the final study treatment administration.
15. Subject agrees not to participate in another interventional study while receiving study treatment in the present study (subjects who are currently in the follow-up period of an interventional clinical study are allowed).

5.2 Exclusion Criteria

Subject will be excluded from participation in the study if any of the following apply:

1. Subject weighs < 45 kg at Screening.
2. Subject has received investigational therapy within 21 days prior to start of IP. (A subject with EGFR activating mutations or a subject with an ALK mutation is allowed to remain on an investigational EGFR TKI or ALK inhibitor until 4 days prior to initiation of IP administration.)
3. Subject requires or has received systemic steroid therapy or any other immunosuppressive therapy within 14 days prior to IP administration. Subjects using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone, 2 mg per day of dexamethasone or up to 10 mg per day of prednisone) are allowed. Note: Corticosteroids for prophylaxis (e.g., contrast dye allergy) or for brief treatment of conditions not related to study treatment (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is also allowed.
4. Subject has symptomatic CNS metastases or subject has evidence of unstable CNS metastases even if asymptomatic (e.g., progression on scans). Subjects with previously treated CNS metastases are eligible, if they are clinically stable and have no evidence of CNS progression by imaging for at least 28 days prior to start of study treatment and are not requiring immunosuppressive doses of systemic steroids (> 30 mg per day of hydrocortisone, > 2 mg per day of dexamethasone or > 10 mg per day of prednisone or equivalent) for longer than 14 days.
5. Subject has leptomeningeal disease as a manifestation of the current malignancy.
6. Subject has an active autoimmune disease. Subjects with type 1 diabetes mellitus, stable endocrinopathies maintained on appropriate replacement therapy and skin disorders (e.g., vitiligo, psoriasis or alopecia) not requiring systemic treatment are allowed.
7. Subject was discontinued from prior immunomodulatory therapy due to a Grade ≥ 3 toxicity that was mechanistically related (e.g., immune-related) to the agent in the judgment of the investigator.

8. Subject has known history of serious hypersensitivity reaction to a known ingredient of ASP1948 or severe hypersensitivity reaction to treatment with another monoclonal antibody.
9. Subject is positive for Hepatitis B virus (HBV) antibodies and surface antigen (including acute HBV or chronic HBV) or Hepatitis C virus ([HCV] RNA). Hepatitis C RNA testing is not required in subjects with negative Hepatitis C antibody testing. HBV antibodies are not required in subjects with negative Hepatitis B surface antigen (HBsAg).
10. Subject has received a live vaccine against infectious diseases within 28 days prior to initiation of study treatment.
11. Subject has a history of drug-induced pneumonitis (interstitial lung disease) or currently has pneumonitis.
12. Subject has an active infection requiring systemic therapy (e.g., intravenous antibiotics) within 14 days prior to IP treatment.
13. Subject is expected to require another form of antineoplastic therapy while on study treatment.
14. Subject has an uncontrolled intercurrent illness including, but not limited to cardiac arrhythmia or psychiatric illness/social situations that would limit compliance with study requirements.
15. Subject's AEs (excluding alopecia) from prior therapy have not improved to Grade 1 or baseline within 14 days prior to start of study treatment.
16. Subject has significant cardiovascular disease including:
    - Subject has inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg on antihypertensive medications).
    - Subject has a history of myocardial infarction or unstable angina within 6 months prior to Cycle 1 Day 1.
    - Subject has New York Heart Association Class II or greater chronic heart failure.
    - History of CVA or TIA within 6 months prior to study treatment.
    - Subject has significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to study treatment.
17. Subject has a history of hemoptysis (bright red blood of 2 mL or more per episode) within 12 weeks prior to study treatment.
18. Subject has evidence of a bleeding diathesis or significant coagulopathy.
19. Subject has inadequate recovery from prior surgical procedure or has had a major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to study treatment, or anticipates the need for a major surgical procedure during the course of the study or minor surgery within 7 days of starting study treatment.
20. Subject has initiated new treatment with medications that affect the coagulation cascade with an INR ≥ 2 such as vitamin K antagonists, heparins and direct thrombin inhibitors or the use of factor Xa inhibitors within 28 days prior to the start of study treatment. Note: If the subject started receiving such medications more than 28 days prior to the

start of study treatment and needs to continue, this is allowed. However, new anticoagulation may not be initiated within 28 days prior to the start of study treatment.

21. Subject has any condition that, in the investigator's opinion, makes the subject unsuitable for study participation.

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

5.3 Restrictions During the Study

Not applicable.

5.4 Screen Failures

A screen failure is defined as a potential subject who signed the informed consent form (ICF), but did not meet 1 or more criteria required for participation in the study and was not enrolled.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic case report form (eCRF).

5.4.1 Rescreening

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, electrocardiogram [ECG], etc.) may be repeated once within the 28-day screening period without the need to register the subject as a screen failure. If more than 28 days elapses from the date of signing the ICF, the subject must be documented as a screen failure. In order to rescreen, a new ICF must be signed and the subject entered into screening with a new subject identification number. Rescreening is only allowed once for an individual subject.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administered

Table 7 Investigational Product

Name	ASP1948
Use	Test product
Dosage Formulation	Solution for injection
Physical Description	Clear colorless to slightly brown and/or yellow color
Unit Dose Strength	1200 mg (Q2W), 2000 mg (Q2W) and 3000 mg (Q3W)
Packaging and Labeling	[redacted] CCI
Route of Administration	Intravenous infusion
Administration Instruction	Administered intravenously over 60 minutes (-5 minute/+20 minute window). IP can be administered before or after meals.
IMP or Non-IMP	IMP
Sourcing	[redacted] CCI

IMP: investigational medicinal product

Refer to the pharmacy manual for detailed information regarding preparation, handling and storage of the IP.

6.1.1 Investigational Product(s) Preparation and Administration

IP will be administered by trained and qualified healthcare professionals in an appropriately supervised healthcare institution setting. Medical equipment and supplies needed for potential IRRs (corticosteroids, epinephrine, antihistamines, intravenous fluids, aerosolized bronchodilators and oxygen, as well as intubation and tracheostomy equipment and a defibrillator) must be readily available in any area where IP is administered. Doses will be administered to the subjects via intravenous infusion using a calibrated infusion pump for the 3 dose levels, as outlined in Table 8.

Table 8 Investigational Product Preparation and Administration

ASP1948 Dose	Number of Vials	Total Administration Volume	Apparatus
1200 mg	5	250 mL	250 mL intravenous bag
2000 mg	8	500 mL	500 mL intravenous bag
3000 mg	12	535 mL	500 mL intravenous bag

At the end of administration, flush with normal saline using 1 flush volume to ensure that the total diluted IP solution has been administered to the subject within the allowed administration window.

The start and stop times of IP infusion, including the flush time, will be documented. If the IP is interrupted due to an infusion reaction, such that the time from IP preparation exceeds 4 hours, then the administration must be discontinued.

Based on compatibility assessments, the acceptable materials for syringes, diluent infusion bags, infusion tubing and in-line or add-on filters are described in Table 9 .

Table 9 Product Contact Materials Tested and Concluded to be Compatible with ASP1948 Diluted in 0.9% Sodium Chloride Solution

Item	Material
Syringe	polypropylene
0.9% NaCl diluent intravenous bag (250 mL and 500 mL bags)	polyvinylchloride or polypropylene
Infusion tubing	polyethylene-lined polyvinylchloride/polyethylene, or polyvinylchloride
In-line or add-on filter (pore size of 0.2 to 0.22 μm)	polyethersulfone/polyethersulfone positively charged

NaCl: sodium chloride

6.1.2 Observation During and After Subject's Dose of Investigational Product

In principle, subjects must be hospitalized from Cycle 1 Day 1 (first dose of ASP1948) to Cycle 2 Day 14 for Dose level A and Dose level B, or Cycle 1 Day 1 (first dose of ASP1948) to Cycle 1 Day 21 for Dose level C. If it is deemed possible to follow a subject on an outpatient basis based on his/her physical condition, etc. during the DLT observation period, the investigator must ensure his/her safety under outpatient management by performing the tests considered clinically necessary before discharge (observation and evaluation of general condition, blood tests, etc.). For the next 3 doses (third, fourth and fifth infusions for Dose level A and Dose level B or second, third and fourth infusions for Dose level C), subjects should remain at the site facility for at least 2 hours after completion of ASP1948 administration. The subject should be instructed to notify site personnel if he/she develops any AEs during this time period.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at API or sponsor's designee in accordance with API or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines and applicable local laws/regulations.

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.

Refer to the pharmacy manual for detailed information regarding packaging and labeling of the IP.

6.2.2 Handling, Storage and Accountability

ASP1948 will be stored in a freezer at [redacted] in a secure location until ready to use. ASP1948 should be protected from light. All unused vials must be kept in their original carton. After ASP1948 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) should not exceed 24 hours, with a maximum time at room temperature of 4 hours. Refer to the pharmacy manual for additional information on IP handling.

The head of the study site or the test product storage manager should take accountability of the test product as following issues:

- The drug storage manager should store and take accountability of the IP as per the procedures for handling the IP written by the sponsor.
- The drug storage manager should prepare and retain records of the IP's receipt, inventory at the study site, use by each subject, and return of unused IP to the sponsor or alternative disposal. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the IP and subjects.
- The drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified in the protocol and reconcile all IP supplied from the sponsor.

6.3 Randomization and Blinding

Not applicable.

6.4 Investigational Product Compliance

The dose and schedule of ASP1948 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, plus accountability for ASP1948 at every cycle will be used to assess compliance with the treatment.

Treatment compliance should be monitored closely and deviation in compliance should be reported to the sponsor.

6.5 Missed Doses

In the case that IP cannot be administered at a scheduled visit, it should be administered as soon as possible. Tumor assessments should continue as per protocol (every 8 weeks from Cycle 1 Day 1 for Dose level A and Dose level B, or every 9 weeks from Cycle 1 Day 1 for Dose level C) even if dosing is delayed. Subjects with infusion delays > 12 weeks from the end of prior treatment cycle should discontinue treatment and have an End of Treatment visit.

6.6 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

6.6.1 Previous Treatment (Medication and Nonmedication Therapy)

Previous treatment is defined as medications and therapies used before the start of study treatment.

The investigation period and items to be entered in the eCRF for previous treatment are shown below.

Previous Treatment	Investigation Period	Items to be Entered in the Electronic Case Report Form
Antitumor medications related to the primary cancer	Day of diagnosis of primary cancer to before the start of study treatment	Drug name, delivery route, duration of use, dose per administration, dose frequency, reason for premature discontinuation, and best overall response
Radiation therapy related to the primary cancer		Type of radiation therapy, area, and duration of use
Procedures related to the primary cancer		Name of procedure and date of use
All medications other than the above	28 days before the start of study treatment to before the start of study treatment	Drug name, delivery route, duration of use, and reason for use
All nonmedication therapies other than the above		Name of therapy, duration of use, and reason for use

6.6.2 Concomitant Treatment (Medication and Nonmedication Therapy)

Concomitant treatment is defined as medications and therapies used after the start of study treatment.

The investigation period and items to be entered in the eCRF for concomitant treatment are shown below. It is not necessary to enter concomitant treatment medications and therapies not used for direct therapeutic purpose, such as contrast media and diluents.

Concomitant Treatment	Investigation Period	Items to be Entered in the Electronic Case Report Form
New anticancer treatments for primary cancer	Start of study treatment to the end of safety follow-up (90 days from last dose) or until initiation of a new anticancer treatment, whichever comes first	Name of therapy, start date, and reason for use
All medications other than the above	Start of study treatment to the end of safety follow-up (30 days from last dose) or until initiation of a new anticancer treatment, whichever comes first	Drug name, delivery route, duration of use, and reason for use
All nonmedication therapies other than the above		Name of therapy, duration of use, and reason for use

- *Investigational agents:* The use of investigational agents is not allowed during study treatment.
- *Steroids and other immunosuppressive therapy:* The use of immunosuppressive agents and immunosuppressive doses of systemic steroids (> 30 mg/day of hydrocortisone, > 10 mg/day of prednisone, > 2 mg/day of dexamethasone or equivalent) is not allowed during study treatment unless needed to manage AEs related to study treatment. The use of topical, ocular, intra-articular, intranasal and inhaled corticosteroids (with minimal systemic absorption) is allowed. Physiologic replacement doses of systemic corticosteroids (≤ 30 mg/day of hydrocortisone or ≤ 10 mg/day of prednisone or equivalent) are permitted. Corticosteroids for prophylaxis (e.g., contrast dye allergy) or for brief treatment of conditions not related to study treatment (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is also allowed.
- *Vaccines:* Live vaccines are prohibited while the subject is receiving study treatment and for 14 days after last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, Bacillus Calmette-Guerin (BCG) and typhoid vaccine.
- *Other Anticancer treatment:* The use of other anticancer therapy (e.g., chemotherapy, hormonal therapy, immunotherapy, radiotherapy, biological therapy and targeted therapy) is not allowed during study treatment; however, (1) subjects with mCRPC who do not have orchiectomy should continue ADT during the study and (2) subjects with breast cancer on endocrine or human EGFR 2 therapy should continue those therapies during the study.

  Palliative (limited field) radiation therapy for bone metastases is allowed. Study treatment should be interrupted during radiation therapy. The use of bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors for bone metastases are allowed if initiated prior to study entry.

  Surgical treatment of isolated or symptomatic lesions for palliation or curative management is also allowed.

- *Other:* Hematopoietic factor products used for primary prevention (only prohibited during the DLT observation period).

6.7 Dose Modification

IP-related toxicity can result in the interruption or discontinuation of IP based on the discretion of the investigator.

6.7.1 Toxicities Requiring Permanent Discontinuation of ASP1948 Treatment

ASP1948 treatment will be permanently discontinued for the following toxicities that are assessed as related to ASP1948, if there is a reasonable possibility that the event may have been caused by ASP1948:

- Hematological toxicity requiring ASP1948 treatment interruption that does not recover to Grade 0 or 1 within 4 weeks
- AST or ALT > 5 × ULN (Grade ≥ 3) in subjects without liver metastases
- AST or ALT > 8 × ULN in subjects with liver metastases
- AST or ALT > 3 × ULN and TBL > 2 × ULN (in subject with Gilbert's syndrome: AST or ALT > 3 × ULN and direct bilirubin > 1.5 × ULN)
- TBL > 3 × ULN
- Grade ≥ 3 nonhematological AE except for Grade 3 rash that has improved to Grade 0 or 1 or Grade ≥ 3 endocrinopathies that are managed to Grade 0 or 1 with replacement therapy.
- Persistent Grade ≥ 2 AEs requiring ASP1948 interruption that do not recover to Grade 0 or 1 within 12 weeks after the last dose with steroid treatment tapered to physiological replacement doses (≤ 10 mg prednisone or equivalent) of study treatment. However, subjects with a persistent Grade ≥ 2 AE requiring ASP1948 interruption may continue on study treatment if asymptomatic and controlled, with investigator and sponsor agreement
- Grade ≥ 2 pneumonitis
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- Grade ≥ 2 encephalopathy, meningitis or Grade ≥ 2 motor or sensory neuropathy
- Any toxicity that results in the inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Grade 3 or 4 IRRs

6.7.2 Toxicities Requiring ASP1948 Treatment Interruption

ASP1948 treatment will be withheld for the following toxicities if there is a reasonable possibility that the event may have been caused by ASP1948:

- 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 rash or Grade 3 endocrinopathies

- AST or ALT ≥ 3.0 and ≤ 5.0 × ULN or TBL > 1.5 and ≤ 3× ULN (in subject with Gilbert's syndrome: AST or ALT ≥ 3.0 and ≤ 5.0 × ULN or direct bilirubin > ULN) in subjects without liver metastases
- AST or ALT ≥ 3.0 and ≤ 8.0 × ULN or TBL > 1.5 and ≤ 3 × ULN (in subjects with Gilbert's syndrome: AST or ALT ≥ 5.0 and ≤ 8.0 × ULN or direct bilirubin > ULN) in subjects with liver metastases
- Any Grade 2 or higher irAE (including but not limited to those listed below):
  - colitis or diarrhea
  - hypophysitis
  - adrenal insufficiency
  - nephritis
  - ocular inflammatory toxicity
  - pancreatitis
  - new-onset neurological symptoms or signs (other than Grade 2 or higher encephalopathy, meningitis or Grade 2 or higher motor or sensory neuropathy, which require permanent discontinuation of ASP1948 treatment)
  - IRR

Additionally, ASP1948 treatment may be interrupted for any AE, laboratory abnormality or intercurrent illness that in the judgment of the investigator warrants delaying dosing of ASP1948.

6.7.3 Criteria for Resuming Study Treatment

Dosing may be delayed for up to 12 weeks from the end of the prior treatment cycle for recovery of toxicity requiring IP treatment interruption. IP treatment may be resumed if the AEs have recovered to Grade 0 or 1 and steroid treatment tapered to physiological replacement doses (≤ 10 mg per day prednisone or equivalent) and do not meet the criteria for permanent discontinuation of study treatment. Interruption for COVID-19-related illness is limited to 12 weeks. Study treatment may be resumed in the absence of COVID-19-related symptoms per investigator judgement.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 Radiographic Assessment

Disease response and progression will be evaluated in this study using the RECIST 1.1 [Eisenhauer et al, 2009] and iRECIST criteria [Seymour et al, 2017] as assessed by the investigator.

Tumor assessments will be performed at Screening and at every 8 weeks (± 1 week) for Dose level A and Dose level B or every 9 weeks (± 1 week) for Dose level C from Cycle 1 Day 1 until confirmed disease progression by iRECIST ("immune" confirmed progressive disease [iCPD])". The assessment will include tumor measurements for target lesions, nontarget lesions and assessment for any new lesions. An overall assessment will be characterized for that time point.

CT or MRI scans are preferred for this study and to ensure comparability, the same technique (CT/MRI) used at Screening should be utilized throughout the study. The same method should be employed and assessed by the same individual on each occasion, when possible. Imaging should include chest, abdomen and pelvis as well as any other anatomical region appropriate for the subject's disease.

Imaging should be performed every 8 weeks or 9 weeks from Cycle 1 Day 1 regardless of treatment interruption or delays. Scans performed prior to informed consent as standard of care are acceptable as screening scans if performed within 28 days prior to Cycle 1 Day 1.

Confirmatory scans for complete response (CR) or partial response (PR) should be performed at least 4 weeks after the date of the scan in which CR or PR was first observed. Confirmatory scans for PD must be performed at least 4 weeks after the date of the scan in which PD was first observed, but no longer than 8 weeks.

Disease progression sites (including target, nontarget, new target, and new nontarget lesions) will be recorded in the eCRF.

7.1.2 Evaluation of Response at Each Time Point

The result of target lesion response, nontarget lesion response, new target lesion response, new nontarget lesion response and overall response assessment at each time point will be recorded in the eCRF according to the iRECIST.

7.1.3 Best overall response

Best overall response (BOR) on the study regimen should be assessed at the end of treatment for each subject according to RECIST 1.1 and iRECIST.

7.1.4 Tumor Response

Tumor size is defined as the sum of the diameters of all target lesions per RECIST 1.1. The percent change from baseline in tumor size will be calculated for subjects with target lesions at baseline. The best percent change in tumor size is the maximum percent reduction from

baseline, or if the subject has no reduction in size, the minimum percent increase from baseline.

7.2 Safety Assessments

Study procedures and their timing are summarized in the Schedule of Assessments (Table 1, Table 2, Table 3 and Table 4). Protocol waivers or exemptions are not allowed.

Procedures conducted as part of a subject's routine clinical management (i.e., standard of care) obtained before signing the ICF may be utilized for Screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame, as defined in the Schedule of Assessments.

7.2.1 Dose Limiting Toxicity (DLT)

Refer to [Section 4.1.4 Dose Limiting Toxicity Criteria].

7.2.2 Adverse Events

See [Section 7.3 Adverse Events and Other Safety Aspects**]** for information regarding AE collection and data handling.

7.2.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving IP is accompanied by increases in liver function test (LFT) values (e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

7.2.3 Laboratory Assessments

Routine laboratory samples for complete blood count (CBC) with differential, serum chemistry, Hepatitis B and C testing, coagulation, urinalysis, urine or serum pregnancy, thyroid stimulating hormone (TSH) and free thyroxine (T4), testosterone and prostate specific antigen (PSA) (mCRPC only) will be collected and analyzed at the local laboratory. Laboratory assessments will be conducted and recorded at visits as outlined in the Schedule of Assessments. The local laboratory must be accredited to perform the protocol-required tests and a certificate of accreditation and laboratory normal ranges must be provided to the sponsor. See [Appendix 12.7 Laboratory Assessments] for the list of clinical laboratory tests to be performed and refer to the Schedule of Assessments (Table 1, Table 2, Table 3 and Table 4) for timing and frequency.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or subinvestigator who is a qualified physician.

7.2.4 Vital Signs, Height and Weight

Vital signs will include systolic and diastolic blood pressure (mmHg), radial pulse (beats/min) and temperature and will be obtained and recorded at the times specified in the

Schedules of Assessments (Table 1 and Table 2). All vital signs will be measured with the subject in the sitting or supine position.

Height and weight will be measured using standard institution practice and equipment and recorded at the times specified in the Schedules of Assessments (Table 1 and Table 2). 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.

7.2.5 Physical Examination

Physical examinations will be conducted and recorded at visits as outlined in the Schedule of Assessments (Table 1 and Table 2).

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems. Genitourinary and rectal system examinations are to be performed only if clinically indicated.

As a result of auscultation, a chest X-ray examination, sialylated carbohydrate antigen (Krebs von den Lungen-6) and transcutaneous arterial oxygen saturation may be performed if clinically indicated.

New or worsening clinically significant findings on physical examination will be recorded as AEs if they meet the criteria in [Appendix 12.4.1 Definition of Adverse Events].

7.2.6 Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be conducted and recorded at visits as outlined in the Schedule of Assessments (Table 1 and Table 2).

The ECOG scale [Oken, 1982] will be used to assess performance status [see Appendix 12.12 Eastern Cooperative Oncology Group Performance Status Scale].

7.2.7 Electrocardiogram

ECGs will be conducted at visits as outlined in the Schedule of Assessments (Table 1, Table 2, Table 3 and Table 4). All recorded ECGs will be transmitted electronically for central reading.

ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semirecumbent, if supine is not tolerated) for 10 minutes before the first ECG from a triplicate or single ECG. For ECGs performed in triplicate, there should be at least 2 minutes between each ECG.

7.2.8 Order of Assessments

The following order should be followed 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. ECG
2. Vital signs (blod pressure and heart rate)
3. 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

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up or Reporting].

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or SAE.

7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information

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 IP. AE collection begins after the signing of the ICF and will be collected until 30 days after the final IP administration or initiation of a new anticancer treatment, whichever comes first, or until the subject is determined to be a screen failure. SAEs (regardless of causality) will be collected from the time of informed consent through 90 days following the last dose of IP or until initiation of a new anticancer treatment, whichever comes first, or until the subject is determined to be a screen failure.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

An AE with a change in severity is recorded as a new AE.

7.3.3 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 7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information]), an AE progresses to an SAE, or the investigator learns of any (S)AE (serious adverse event or adverse event) including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify the sponsor.

7.3.4 Reporting of Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential, so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

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

Procedures for reporting SAEs to the sponsor are described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

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 7.1 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between IP and the event, it should be reported as an (S)AE. All deaths up to 90 days after the final administration of IP must be reported as an SAE, even if attributed to disease progression.
- Preplanned and elective hospital/clinical procedures/interventions or procedures for diagnostic, therapeutic or surgical procedures for a preexisting condition that did not worsen during the course of the clinical study. These procedures are collected per the eCRFs Completion Guidelines.

7.3.6 Adverse Events of Special Interest

IRRs are considered AEs of special interest. Subjects should be evaluated carefully for potential IRRs as described in [Section 2.1.2.1.1 Infusion-related Reactions]. In the event a subject is diagnosed with an IRR, then it should be reported as an AE using the diagnosis rather than the list of symptoms. 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 JUTOKUNA YUUGAIJISHOU HOUKOKUSHO and reported within 24 hours as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

7.3.7 Special Situations

Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are collected in the eCRF, as protocol deviation per [Section 10.3 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 the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on JUTOKUNA YUUGAIJISHOU HOUKOKUSHO.

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

Instructions and procedures for reporting special situations are provided in [Appendix 12.4.6 Reporting Procedures for Special Situations].

7.3.8 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the study properly, the sponsor will inform all investigators involved in the study as well as the appropriate regulatory authorities. Investigators should inform the IRB 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 study.

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all investigators involved in the study, head of the study site and appropriate regulatory authorities of such information. The head of the study site who receives such information will decide whether the study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Appendix 12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information].
2. In addition, when the head of the study site receives the revisions of the IB, protocol, written information, information on the matters covering the quality of the test product, efficacy and safety, information necessary for conducting the study properly or documents to be examined by the IRB, these documents should be sent to the IRB.

7.3.9 Urgent Safety Measures or Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Subjects

An urgent safety measure (USM) is an intervention that 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 competent authorities (CA), IRB, where applicable, in order to protect subjects from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study site. Keep a copy of the notice.
2. Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the sponsor.

7.3.10 Reporting Urgent Safety Measures

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

If the event is confirmed to be a 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 study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB within timelines set by regional regulations.

7.4 Pharmacokinetics

Serum concentrations of ASP1948 will be extensively evaluated in Cycle 1 and sparsely in the subsequent cycles. The details of sample collection for pharmacokinetic assessments are shown in the Schedule of Assessments (Table 1, Table 2, Table 3 and Table 4).

Blood samples will be collected from a vein or port that is not used for drug infusions. Blood sampling, processing, storage and shipment instructions are provided in a laboratory manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory. Samples remaining after pharmacokinetic assessments may be used for immunogenicity analysis as described in [Section 7.5.4 Immunogenicity Assessment], or for additional exploratory biomarker analysis as described in [Section 7.5.1 Biomarkers].

7.5 Pharmacodynamics | Immunogenicity

7.5.1 Biomarkers

The tumor tissue and blood/serum/plasma samples described in [Sections 7.5.2 Peripheral Blood Biomarkers and 7.5.3 Tumor Tissue Samples] may be used for research purposes to identify genomic/transcriptomics and/or proteomics biomarkers that may be associated with clinical outcome or dynamic changes associated with ASP1948 treatment (in terms of dose, safety, tolerability and efficacy). Since the identification of exploratory biomarkers that correlate with the efficacy or safety of ASP1948 treatment may continue to evolve as findings becomes available, additional analyses related to ASP1948 effects on the subject's immune system or clinical outcomes may be conducted. Analysis results of biomarker research will not be disclosed to subjects, because the biomarkers to be tested are highly exploratory and their clinical significance is unknown. Based on exploratory nature of the obtained data, the prediction may not be accurate or reliable. The tumor tissue and blood/serum/plasma samples remaining after the specified biomarker assessments (e.g., aliquots of tumor cell RNA or DNA, PBMCs) may be used for retesting in additional analyses as defined above related to prediction of response or dynamic changes associated with ASP1948 treatment. The tumor tissue and blood/serum/plasma samples (e.g., aliquots of tumor cell RNA or DNA, PBMCs) will be stored at the study sponsor's facility or a contract laboratory facility for up to 15 years after database closure, at which time the samples will be destroyed. The tumor tissue and blood/serum/plasma samples will be destroyed, in principle, if the subject withdraws his/her consent during the study period. However, if the analysis results have already been obtained, they may be used. The procedures for the collection, handling and shipping of laboratory samples being submitted to the central laboratory will be specified in a laboratory manual.

7.5.2 Peripheral Blood Biomarkers

Blood samples will be collected according to the Schedule of Assessments (Table 1, Table 2, Table 3 and Table 4).

Serum and plasma samples may be analyzed for biomarkers including but not limited to immune-related chemokines, cytokines, circulating soluble cancer biomarkers, cell free DNA/RNA and other soluble factors. Blood samples may be analyzed for biomarkers including but not limited to lymphocyte subsets and target RO on PBMCs.

7.5.3 Tumor Tissue Samples

Archival tumor specimens are encouraged but not mandatory. A minimum of 1 formalin-fixed paraffin embedded (FFPE) tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 10 FFPE unstained serial slides are required.

7.5.4 Immunogenicity Assessment

Blood samples for ASP1948 immunogenicity analysis will be collected from all subjects according to the Schedule of Assessment (Table 1, Table 2, Table 3 and Table 4). Samples will be evaluated for development of immunogenicity in subjects. Sample processing,

storage and shipment instructions will be provided in the laboratory manual. Samples remaining after ASP1948 immunogenicity assessments may be used for additional exploratory biomarker analysis as described in [Section 7.5.1 Biomarkers].

7.6 Electronic Clinical Outcome Assessment

Not applicable.

7.7 Other Assessments

7.7.1 Sample for Banked Pharmacogenetic Sample Analysis

Pharmacogenetic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety. A 4 mL sample of whole blood for possible banked PGx analysis will be collected as indicated in the Schedule of Assessments (Table 1 and Table 2). Samples will be shipped to a sponsor-designated banking contract research organization (CRO).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.8 Pharmacogenomic Analysis With Banked Sample] for further details on the banking procedures.

7.8 Total Amount of Blood

The total amount of blood for each subject will vary depending on the course of their disease, duration on treatment and local laboratory requirements. At any time during the study, if an unscheduled test or follow-up of laboratory test values becomes necessary or if an AE occurs, additional blood may be drawn for safety monitoring.

The approximate amount of blood to be collected for each purpose of use is shown below:

- Hepatitis virus: 8 mL per sample
- CBC with differential: 2 mL per sample
- Serum chemistry: 7 mL per sample
- Coagulation: 3 mL per sample
- Thyroid function test: 2 mL per sample
- Serum pregnancy test: 0.5 mL per sample
- Testosterone (mCRPC only): 2 mL per sample
- PSA (mCRPC only): 2 mL per sample
- Whole blood - immune cell subsets (flow cytometry), and receptor occupancy: total 4 mL per sample
- Serum for circulating soluble factors and cytokines/chemokines and oncomarker: 6 mL per sample
- Serum for pharmacokinetics: 2.5 mL per sample
- ADA measurement: 3.5 mL per sample
- Whole blood sample for PGx (optional): 4 mL per sample

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s) From Study Treatment

A discontinuation from treatment is defined as a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The 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 discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The reason for discontinuation from study treatment must be documented in the subject's medical records.

A subject must discontinue study treatment for any of the following reasons:

- Disease progression, as defined by the following:
  - Confirmed disease progression by iRECIST (iCPD)
  - Disease progression by RECIST 1.1 (unconfirmed progression by iRECIST, denoted "immune unconfirmed progressive disease [iUPD]) and the subject is not clinically stable to await subsequent confirmatory scan [see Section 8.1.1 Criteria for Continuing Treatment Past RECIST 1.1 Disease Progression].
  - Clinical Disease Progression per investigator's assessment
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable AEs.
- Subject requests to stop treatment.
- Any clinical AE, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject
- Subject is lost to follow-up.
- Female subject becomes pregnant.
- Subject remains noncompliant with the protocol based on the investigator's or sponsor's assessment.
- A subject who has a confirmed CR by 2 scans ≥ 4 weeks apart and who has been on study treatment for at least 12 cycles for Dose level A and Dose level B or 8 cycles for Dose level C may discontinue study treatment at the discretion of the investigator after receiving at least 2 doses beyond the initial determination of CR.
- Treatment interruption of > 12 weeks from the end of the prior treatment cycle.
- Subject completes the 2-year treatment period.

8.1.1 Criteria for Continuing Treatment past RECIST 1.1 Disease Progression (iUPD)

In accordance with iRECIST guidelines [Seymour et al, 2017], treatment beyond initial RECIST 1.1-defined progression (i.e., iUPD) is allowed only for subjects who are clinically

stable; these subjects may continue study treatment until the next imaging assessment, which must occur at least 4 weeks, but no longer than 8 weeks later.

A subject is deemed clinically stable if in the investigator's opinion there are no indications of the following:

- No worsening of performance status.
- No clinically relevant increases in disease-related symptoms such as pain or dyspnea occur that are thought to be associated with disease progression (i.e., no requirement for increased palliative intervention).
- No requirement for intensified management of disease-related symptoms, such as increased analgesia, radiotherapy or other palliative care.

The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the subject before a decision is made about whether or not to continue study treatment. The subject will be reconsented if the decision is made to continue with study treatment. Subjects with iUPD who are not clinically stable should be documented as not clinically stable in the eCRFs.

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in Table 1 and Table 2. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information.

8.2.1 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.

8.3 Discontinuation of the Study Site

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

8.4 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.

9 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 at the latest. Any changes from the analyses planned in the SAP will be justified in the clinical study report (CSR).

In general, continuous data will be summarized with descriptive statistics, frequency and percentage for categorical data.

9.1 Sample Size

The estimated number of evaluable subjects for this study is 18 subjects (6 subjects per dose level). The number of subjects enrolled will be dependent on the DLT incidence. The maximum number of evaluable subjects is 27 (9 subjects per dose level).

Rationale

The sample size for this study is not based on a statistical power calculation but is expected to provide safety and pharmacokinetic information to determine the tolerability of ASP1948.

9.2 Analysis Sets

9.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are enrolled and receive at least 1 dose of IP and have at least 1 post baseline measurement. This will be the analysis set for the efficacy analyses.

9.2.2 Safety Analysis Set

The safety analysis set (SAF) will consist of all subjects who receive at least 1 dose of IP. The SAF will be used for all statistical summaries of the safety data.

9.2.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of the administered population for which at least 1 concentration data is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

9.2.4 Pharmacodynamic Analysis Set

The pharmacodynamic analysis set (PDAS) will consist of the subjects from the administered population for whom sufficient pharmacodynamic measurements were collected. The PDAS will be used for all analyses of pharmacodynamic data.

9.2.5 Dose Limiting Toxicity Evaluation Analysis Set

The DLT evaluation analysis set (DEAS) is defined as all subjects in the SAF, but excluding any subject who meets the following criterion:

- A subject without a DLT who receives less than the prescribed ASP1948 dose in Cycle 1 and Cycle 2 for Dose level A and Dose level B or Cycle 1 for Dose level C, or does not complete Cycle 1 and Cycle 2 for Dose level A and Dose level B or Cycle 1 for Dose level C for a reason other than DLT (e.g., consent withdrawal).

DEAS will be used for the analysis of DLT data.

9.3 Demographics and Baseline Characteristics

9.3.1 Demographics

Demographics and baseline characteristics will be summarized by dose level and overall for all treated subjects.

9.3.2 Subject Disposition

The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all treated subjects and for subjects in the SAF.

9.3.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

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

9.3.4 Medical History

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

9.3.5 Investigational Product Exposure

All IP exposure data will be listed.

9.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS. Tumor related analyses are summarized based on RECIST 1.1 and iRECIST by dose level.

9.4.1 Sum of Diameters

For the subjects with at least 1 measurable lesion, percentage change of sum of diameters (SOD) at post baseline assessment visit from SOD at baseline will be presented as a spider plot and best percentage change of SOD will be presented as a waterfall plot.

9.4.2 Best Overall Response

BOR as per RECIST 1.1 and iRECIST will be listed.

9.4.3 Analysis of Exploratory Endpoints

9.4.3.1 Exploratory Analysis of Potential Biomarkers of ASP1948 Activity

Associations between biomarkers [Section 7.5.1 Biomarkers] and clinical (e.g., efficacy, safety or pharmacodynamics) measures may be performed on subjects in an appropriate

analysis set (e.g., SAF, FAS, PDAS or PKAS) who have sufficient baseline and on-study measurements to provide interpretable results for specific parameters.

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 not specified in the protocol, such as alternative modeling approaches, may be conducted. All analyses described in this section are based on the availability of the data.

9.5 Analysis of Safety

Safety analysis will be conducted on the SAF.

9.5.1 Dose Limiting Toxicities

The number and proportion of subjects with DLTs will be calculated using the DEAS.

9.5.2 Adverse Events

AEs will be coded using MedDRA.

A TEAE is defined as an AE observed after starting administration of the IP and 30 days after the last dose of IP.

The number and percentage of subjects with TEAEs, SAEs, AEs leading to withdrawal of treatment, and AEs related to IP will be summarized by SOC, preferred term and dose level. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

An IP-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator.

9.5.3 Laboratory Assessments

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

Shifts relative to normal ranges from baseline to each time point during treatment period in laboratory tests will also be tabulated. Laboratory data will be displayed in listings.

9.5.4 Vital Signs

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

Vital signs data will be displayed in listings.

9.5.5 Physical Examination

Physical examination results will be listed.

9.5.6 Electrocardiogram

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

The QT corrected by Fridericia's Correction formula (QTcF) interval will be summarized using frequency tables for each treatment visit for values of clinical importance using the range criteria below.

	Corrected QT Interval Criteria Value (msec)
Normal	≤ 450
Borderline	> 450
Prolonged	> 480
Clinically significant	> 500

The QT corrected (QTc) interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit.

Variable	**Change from Baseline**
Corrected QT (QTcF) Interval (msec)	< 0
	≥ 0
	> 30
	> 60

Effects of serum concentrations of ASP1948 on ΔQTcF (defined as the mean change from baseline in QTcF) will be assessed.

9.5.7 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 end of study visit will also be summarized. Negative change scores indicate an improvement. Positive scores indicate a decline in performance.

9.6 Analysis of Pharmacokinetics

Descriptive statistics will include the number of subjects (n), mean, SD, minimum, median, maximum, coefficient of variation (CV), geometric mean and geometric CV, whenever applicable.

9.6.1 Serum Concentration

Serum concentrations of ASP1948 will be listed and summarized using descriptive statistics by scheduled time point. ASP1948 data will be summarized by dose level and cycle. Standard graphics including mean serum concentration-time profiles, overlay (spaghetti) plots and individual subject serum concentration-time profiles on linear and semilogarithmic scales will be produced as appropriate.

Steady state of ASP1948 will be evaluated using a visual inspection of individual subject trough concentrations versus day (spaghetti plot) overlaid with a mean profile.

9.6.2 Estimation of Pharmacokinetic Parameters

The pharmacokinetic parameters will be calculated using Phoenix WinNonlin version 6.4 or higher. Pharmacokinetic parameters will be calculated using a noncompartmental model. Further details on the calculation of the pharmacokinetic parameters will be provided in the SAP. Descriptive statistics will be provided for ASP1948 pharmacokinetic parameters.

9.7 Analysis of Pharmacodynamics | Immunogenicity

Descriptive statistics (e.g., n, mean, SD, minimum, median, maximum, CV, geometric mean and geometric CV) will be provided for pharmacodynamic parameters whenever applicable. Exploratory analysis of the relationship between pharmacodynamic measurements and pharmacokinetics, efficacy and safety in subjects may be performed.

Immunogenicity of ASP1948 will be summarized using the frequency of antidrug antibody-positive subjects on the SAF. The potential relationship between ASP1948 immunogenicity and ASP1948 pharmacokinetics, efficacy and safety profiles in subjects will be explored.

9.8 Other Analyses

9.8.1 Retrospective Analysis of Pharmacogenetics

The content of analysis for retrospective PGx investigation has not been determined at present. In the future, an exploratory study may be conducted to assess whether there is a relationship between the genetic analysis results and the results of this clinical study (clinical information: e.g., drug response, toxicity, survival rate, and pharmacokinetics, etc.). The sponsor will start such a study when the detailed content of the study has been determined. In such a case, the sponsor should prepare the study plan, which has to be reviewed and approved by the ethics committee of the sponsor regarding the appropriateness of the implementation of the study from ethical and scientific standpoints, prior to conduct of the study. The results of this retrospective study will be provided as a separate report, and not be included in the CSR.

9.9 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 10.3 Major Protocol Deviations] will listed.

9.10 Interim Analysis (and Early Discontinuation of the Study)

No formal interim analysis will be performed in this study.

9.11 Additional Conventions

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

The final handling of missing data, outliers and visit windows will be decided before database lock, in reference to the opinions and advice of the DESC and the statistical advisor, as needed. The criteria for handling of analysis time points will be determined by taking acceptable visit windows specified in Table 1 and Table 2 into consideration. Subjects or data excluded from analyses will be listed but excluded from the tabulation of summary

statistics, etc. As a general principle, no imputation of missing data will be performed. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment-emergent. Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown. See the SAP for details of the definition for windows to be used for analyses by visit.

10 OPERATIONAL CONSIDERATIONS

10.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values) in the eCRF within 5 days after the subject's visit (Cycle 1 and Cycle 2 visit data for Dose level A and Dose level B or Cycle 1 visit data for Dose level C are expected to be entered into EDC within 2 days).

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 the source. These documents should be appropriately maintained by the study site.

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

Laboratory tests are performed at both local and central laboratories. The laboratory tests that will be done at the local laboratory include hematology, serum chemistry, coagulation, urine dipstick, urine or serum pregnancy test, TSH and free T4; Hepatitis B and C; testosterone and PSA (mCRPC only). Local laboratory results including oncomarkers performed at the discretion of the investigators will be recorded in the eCRF by the site.

The laboratory tests that will be performed at the central laboratory include immune cell populations (flow cytometry), RO, serum for circulating soluble factors and cytokines/chemokines and oncomarker, pharmacokinetics, ADAs (immunogenicity), tumor tissue analysis including PD-L1 expression and PGx. 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.

ECG results are performed at a central ECG reader, eResearch Technology, Inc. Central ECG-read data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central ECG laboratory will provide the sponsor or designee with a complete and clean copy of the data.

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

For screen failures, the minimum demographic data (sex, birth year and month or age, race and informed consent date), AEs and reason for screen failure will be collected in screen failure log, if applicable. This information will be entered into the study database.

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

The following demographic information will be collected during the screening period and entered in the eCRF:

- Date of informed consent
- Birth year and month
- Sex
- Race
- Information on the target disease (see [Section 10.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease])
- Medical History (see [Section 10.2.2 Medical History])
- Previous treatment history (see [Section 6.6 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)])
- ECOG Performance Status (see [Appendix 12.12 Eastern Cooperative Oncology Group Performance Status Scale])
- Pregnancy test (women of childbearing potential)

10.2.2 Medical History

Diseases that have resolved prior to the date of the informed consent are handled as medical history. For malignancies (except for the primary cancer), diagnosis, the onset date and recovery date will be collected and entered in the eCRF.

Diseases that have not resolved on the date of informed consent are handled as complications. Information on all complications will be collected, and each diagnosis and the onset date will be entered in the eCRF.

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

A complete medical history of the target disease will be collected and entered in the eCRF at Screening. This will include:

- Confirmation of primary cancer diagnosis (date of initial diagnosis, and histology)
- Stage of disease at Screening
- Tumor-specific information
- Tumor-specific therapy history

10.3 Major Protocol Deviations

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

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being 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 subjects.

A major protocol deviation is 1 that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

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 and/or efficacy pharmacokinetic parameters of the subject to determine subject continuation in the study.

The major protocol deviation criteria that will be summarized at the end of the study 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.

The investigator will also assure that deviations meeting IRB and applicable regulatory authority criteria are documented and communicated appropriately. All documentation and communications to the IRB and applicable regulatory authorities will be provided to the sponsor and maintained within the Trial Master File.

10.4 STUDY ORGANIZATION

10.4.1 Dose Escalation and Safety Committee

A DESC ("the committee") consisting of sponsor representatives and investigators will convene after the end of the DLT observation period for all subjects enrolled in each dose level. The sponsor will comprehensively assess the data (including AEs reported for subjects who are unevaluable for DLT), and discuss the tolerability of the current dose with the principal investigator and/or subinvestigators and statistical advisor at the DESC. Based on the results of the discussion, the sponsor will decide the tolerability of the current dose level. The DLT observation period may be extended if deemed appropriate by the DESC.

Detailed procedures will be provided in a separately prepared procedure manual.

10.4.2 Other Study Organization

Refer to Attachment.

10.5 Registration of Subjects

Not applicable.

The investigators will confirm that subjects satisfy the inclusion/exclusion criteria for this study during the screening period.

11 REFERENCES

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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 study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board

Prior to the agreement on this clinical study, the protocol, the IB, and all materials used to obtain informed consent from subjects must be reviewed and approved by the IRB at each study site to ensure that subject's human rights, safety, and well-being are protected. There will be a subsequent conclusion of contracts with the study sites after the approval.

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 and/or revisions. Depending on the nature of the amendment, either IRB or competent authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB and appropriate regulatory authorities followed by the approval of the head of the study site.

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 and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed and signed or placed a personal seal and dated by the subject, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed or sealed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that the ICF was signed prior to any study-related procedures and that the subject received a signed copy of the ICF.

The signed ICFs will be retained by the investigator and made available (for review only) to the study monitor, auditor and appropriate 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 verbally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participating in the study (e.g., report of serious 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. 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 verbally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF or place a personal seal. A copy of the signed or sealed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the reconsent process.

12.1.6 Source Documents

Source data must be available at the study site to document the existence of the 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 electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment and/or drug accountability.

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 be available for archiving.

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. 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 subject's medical records and/or study progress notes.

The records to be retained at the study sites are those listed as essential documents in GCP. These records shall be retained by the head of the study site or the record keeper designated by the head until notice issued by the sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the sponsor or appropriate regulatory authorities.

The head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in (1) or (2) below, whichever comes later.

3. Approval date of marketing of the test drug (if development of the drug is stopped, until 3 years after the decision to discontinue development is notified).
4. Until 3 years after discontinuation or termination of the study.

The following are the major documents to be retained at the study site.

1. Source documents (clinical data, documents and records for preparing the eCRF) hospital records, medical records, test records, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the sponsor, records of clinical coordinators, and records related to the study selected from those verified in other departments or hospitals.
2. Study contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for study (including a request for continuation/amendment), letter of request for review, notice of study contract, study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), curriculum vitae of investigators, list of subinvestigators, list of signatures and print of seals (copy) and eCRF (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the study by the head of the study sites (Article 32-1, Ministry of Health and Welfare Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a study whose period exceeds 1 year or the adequacy of continuously conducting the study from which information on adverse drug reactions is obtained, and other documents obtained. A finalized protocol (including revisions), finalized IB (including revisions), operational procedures for the investigator, materials and

information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation) and the review result report of the IRB (including continuous deliberation), etc.

4. Records of control for IP and other duties related to the study. Procedure for controlling the IP, drug inventory and accountability record, vouchers for the receipt and return of the IP, and the prescriptions for concomitant medications.

The documents of the DESC (minutes and SOPs and others) shall be retained by the sponsor.

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 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 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 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 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 Study

Information concerning the test product, 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 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 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 study agreement.

After agreement between the sponsor and investigator(s), the manuscript can be submitted for publication.

12.1.10 Insurance of Subjects and Others

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

1. If a subject incurs an injury as a result of participation in the study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards a compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the study contract.
4. The sponsor shall make an arrangement for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

12.1.11 Signatory Investigator for Clinical Study Report

The medical advisor and/or 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 signatory will be the medical expert and/or the representative for the coordinating investigator(s) or the principal investigator(s).

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

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

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB and appropriate 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 or appropriate regulatory authorities. The confidentiality of the subject's identity 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 Japan-Asia Data Science department or designee of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by data management. eCRF retrieval and correction process will be referenced in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the WHO Drug Dictionary Enhanced, 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 study at any or all study 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.

To support quality around subject safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study are provided below.

Table 10 Quality Tolerance Limit

QTL #: Name and Parameter	Definition	Parameter Justification
QTL 1: Reliability of evaluation of the tolerability and safety profile (DLT assessment): Number of subjects without any data that affect DLT assessment entered prior to the DESC or with entry error about relevant AE and laboratory data occurred prior to the DESC.	Number of subjects without all relevant AE and laboratory data entered prior to the DESC or with entry error about relevant AE and laboratory data occurred prior to the DESC.	In order to ensure the reliability of primary objective (tolerability and safety), DLTs are needed to be properly assessed. Therefore, all relevant AE and laboratory data should be entered into the database for the entire DLT evaluation period. Number of subjects without all relevant AE and laboratory data entered prior to the DESC or with entry error about relevant AE and laboratory data occurred prior to the DSEC should be 0.

AE: adverse event; DESC: Dose Escalation and Safety Committee; DLT: dose limiting toxicity

QTL Management Activities:

- For control of risks associated with "QTL1: Reliability of evaluation of the tolerability and safety profile (DLT assessment)," refer to [Section 4.1.3 Tolerability Evaluation Procedures, Section 4.1.4 Dose Limiting Toxicity Criteria and Section 10.1 Data Collection].

12.3 Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedule of Assessments. Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A woman is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

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

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than 1 follicle-stimulating hormone (FSH) measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Women on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

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

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 6 months after the final IP administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral
- Other hormonal methods of contraception containing progesterone
    - Intrauterine hormone-releasing system
- Other methods of contraception
    - Intrauterine device
    - Bilateral tubal occlusion
- Vasectomized partner
  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

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

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

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

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 6 months after final drug administration.[a]

- 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.
- Use a condom.
- Female partners of male subjects who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception.

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

12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.4.1 Definition of Adverse Events

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

12.4.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g. hematology, serum chemistry or urinalysis) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), 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.

12.4.1.2 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 (DILI). Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL 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 DILI (potential Hy's Law cases) and are always to be considered important medical events and reported per [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

12.4.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, the event:

- 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).
- 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 one 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.

12.4.3 Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information [Section 2.1.2 Summary of Key Safety Information for Investigational Product] to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The 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 IP 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 IP?"

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 IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered IP?
- Plausibility (i.e., could the event have been caused by the suspect drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
    - Dechallenge: Did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
    - Dose reduction: Did the (S)AE resolve or improve after reducing the dose of the suspect drug?
    - Rechallenge: Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?

- Laboratory or other test results: a specific laboratory investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pretreatment, during and posttreatment).
- Available alternative explanations independent of IP 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.
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible temporal relationship between exposure to the IP and (S)AE onset and/or resolution will be provided. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?

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 investigator always assesses 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 instances, 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.

12.4.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) guidelines version 4.03. The items that are not stipulated in the NCI-CTCAE version 4.03 will be assessed according to the criteria in Table 11 and entered into the eCRF:

Table 11 Grading Scale Defining the Severity of an Adverse Event

Grade	Assessment Standard
1 - Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2 - Moderate	Minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL†
3 - Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting self-care ADL‡
4 - Life threatening	Life threatening consequences, urgent intervention indicated
5 - Death	Death related to AE

ADL: activities of daily living; AE: adverse event

†Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

‡Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

12.4.5 Reporting Procedures for Serious Adverse Events

In the case of an SAE, the investigator or subinvestigator must report to the head of the study site and must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the appropriate regulatory authorities to the sponsor by fax or email immediately (within 24 hours of awareness) and to the head of the hospital.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email JUTOKUNA YUUGAIJISHOU HOUKOKUSHO to:

Astellas Pharma Inc. – Japan
Pharmacovigilance
Fax number: +81-(0)3-3243-5747
Email: rk-safety-jp@astellas.com

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] using the pregnancy reporting form and in the eCRF.

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 the sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for 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.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female subject as an AE in the eCRF or SAE per [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the pregnancy reporting form.

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

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP.
- If an infant dies more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP 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 or other means as appropriate. (S)AE 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.

12.4.6.2 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the subject), overdose or "off-label use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 10.3 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

In the event of suspected ASP1948 overdose, the subject should receive supportive care and monitoring. The medical monitor should be contacted as applicable.

12.4.6.3 Misuse/Abuse

Definition of misuse: Situations where the IP is intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP suspected, the investigator must forward the special situation worksheet to the sponsor 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 an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

12.4.6.4 Occupational Exposure

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

12.4.6.5 (Suspicion of) Transmission of Infectious Agent

If transmission of an infectious agent associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor 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 an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with the details of the suspected transmission of infectious agent.

12.4.6.6 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor 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 an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

12.5 Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of DILI during the course of the study. It should be noted that this section does not specify the end of study analyses of liver enzymes. The end of study liver enzymes analyses will be described in the SAP. Any subject enrolled in a study with active drug therapy and who reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases) or TBL > 2 × ULN should undergo detailed testing for liver enzymes (including at least alkaline phosphatase [ALP], ALT, AST and TBL). 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 ULN is as shown in Table 12 .

Table 12 Moderate and Severe Liver Abnormalities

	ALT or AST		Total Bilirubin
Moderate	> 3 × ULN (in patients without liver metastases), > 5 × ULN (in patients with liver metastases)	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal

†Samples taken simultaneously or within a maximum of 24 hours.

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

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

The investigator may determine that abnormal liver function results, other than those 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 clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal LFTs should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the IP 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 an SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to IP 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" in the eCRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, 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 clinical 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, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

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

† Samples taken simultaneously or within a maximum of 24 hours.

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:

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

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

FDA Guidance for Industry:

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 subjects showing such AT elevations, often with AT levels much greater than 3 × ULN, 1 or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral Hepatitis A, B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Reference

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

12.6 List of Excluded Concomitant Medications

Refer to [Section 6.6 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)].

12.7 Laboratory Assessments

Table 13 details the specific laboratory assessments.

Table 13 Clinical Laboratory Tests

Panel/Assessments	Parameters to be Analyzed
Hepatitis Virus	Hepatitis B virus (HBV) Surface Antigen Immunoglobin M antibody to Hepatitis B core antigen (IgM anti-HBc) (for subjects who test positive for HBsAg) Total antibody to Hepatitis B core antigen (total anti-HBc) (for subjects who test positive for HBsAg) Hepatitis C virus (HCV) Antibody HCV RNA (for subjects who test positive for HCV Antibody)
CBC with Differential	Red blood cell count Hemoglobin Hematocrit White blood cell count Platelet count White blood cell count differentials Absolute neutrophil count Absolute lymphocyte count
Serum Chemistry	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen/blood urea Creatine phosphokinase (CPK) Serum creatinine Calcium Chloride Glucose Lactate dehydrogenase Magnesium Phosphorous Potassium Sodium Total bilirubin (including direct and indirect if available) Total protein
Urinalysis (Standard Urine Dipstick)	Color Appearance Specific gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen

Panel/Assessments	Parameters to be Analyzed
Coagulation	INR (with prothrombin time/prothrombin time percent if reported, or partial thromboplastin time ratio if reported) Activated partial thromboplastin time or partial thromboplastin time
Pregnancy Test – Urine/Serum	Human chorionic gonadotropin (hCG)
Thyroid Function Tests	Thyroid stimulating hormone Free T4
Testosterone (mCRPC only)	Testosterone
Serum Tumor Biomarker	Prostate specific antigen (mCRPC only)
Immune Cell Subsets (flow cytometry)	CD3, CD4, CD8, CD56, CD304(NRP1) etc.
Serum for Cytokine/Chemokine Panel and Soluable Factors	IL-2, IL-4, IL-6, IL-8 etc.
Oncomarker	AFP, CA-125, CA 15-3, CA 19-9, CEA etc.

CBC: complete blood count; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; iCPD: immune-confirmed progressive disease; IgM: immunoglobulin M; INR: international normalized ratio; mCRPC: metastatic castration resistant prostate cancer; T4: thyroxine

12.8 Pharmacogenomic Analysis With Banked Sample

INTRODUCTION

PGx 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 kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

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.

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 the 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 approximately 4-mL sample of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped to a designated banking CRO as directed by Astellas.

PHARMACOGENETIC 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 PHARMACOGENETIC SAMPLES/DATA

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

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the 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.

12.9 Monitoring for Potential Immune-related Adverse Events

Potential irAE	**Closely monitor subjects' symptoms for prompt diagnosis and management**
Pneumonitis	New cough, worsening cough, shortness of breath or chest pain
Colitis	Changes in bowel habits; abdominal pain; blood or mucus in stool; nausea
Hepatitis	Yellowing of skin or whites of eyes; pain on right side of abdomen; dark urine (color of tea); nausea or vomiting; bleeding or bruising more easily than usual; loss of appetite; drowsiness
Endocrinopathies	Persistent or unusual headaches, changes in vision, rapid heartbeat, increased sweating, feeling very tired or weak, achy muscles, change in weight (gain or loss), feeling lightheaded or feeling faint, feeling more hungry or thirsty than usual, loss of hair, mood changes such as reduced sex drive or increased irritability, forgetfulness, feeling cold, constipation, deeper voice, urinating more frequently than usual, nausea or vomiting, abdominal pain
Motor/sensory neuropathy; Encephalitis; Myasthenia syndrome/myasthenica gravis or Guillain-Barré syndrome	Numbness or tingling, weakness, confusion, headache, forgetfulness, changes in mood or behavior, fever, increased sensitivity to light, neck stiffness
Ocular Inflammation	Changes in vision (blurry vision; double vision; other vision changes), eye pain, eye redness, eyelid swelling
Pancreatitis	Nausea or vomiting, abdominal pain
Infection	Fever, other signs of infection
Musculoskeletal inflammation	New or worsening joint symptoms, muscle weakness or pain

irAE: immune-related adverse event

Note: These events have not been observed in the nonclinical studies with ASP1948, but have been observed in clinical studies with other immune checkpoint inhibitors.

12.10 Guidelines for Management of Potential Immune-related Adverse Events

CTCAE Grade IrAE	**Guidelines for Management**
Grade 1	• Continue ASP1948 and closely monitor the subject.
Grade 2	• Withhold ASP1948 until toxicity improves to ≤ Grade 1. • Corticosteroids (initial dose of 0.5 to 1 mg/kg per day of prednisone or equivalent) may be administered. • Taper corticosteroids over 4 to 6 weeks.
Grade 3	• Withhold ASP1948 until toxicity improves to ≤ Grade 1. • Administer high-dose corticosteroids (prednisone 1 to 2 mg/kg per day or methylprednisolone intravenously 1 to 2 mg/kg per day). • If symptoms do not improve with 48 to 72 hours of high-dose corticosteroids, infliximab may be administered. • Taper corticosteroids over 4 to 6 weeks.
Grade 4	• Stop ASP1948 immediately and permanently discontinue the subject.* • Administer high-dose corticosteroids (prednisone 1 to 2 mg/kg per day or methylprednisolone intravenously 1 to 2 mg/kg per day) until toxicity improves to ≤ Grade 1. • Taper corticosteroids over 4 to 6 weeks.

CTCAE: National Cancer Institute Common Toxicity Criteria; IrAE: immune-related adverse event

*Subjects with controlled endocrinopathies with hormone replacement may resume ASP1948 under the discretion of the investigator.

Source: Brahmer JR, Lacchetti C1, Schneider BJ1, Atkins MB1, Brassil KJ1, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36(17):1714-68.

12.11 Guidelines for Standard Infusion-related Reactions and Anaphylaxis

NCI-CTCAE Grade Infusion Reaction	Guidelines for Management
Grade 1 standard infusion reactions	• Continue infusion and closely monitor subject (described in [Section 6.1.2 Observation During and After Subject's Dose of Investigational Product])

Grade 2 standard infusion reactions	• For Grade 2: Interrupt infusion until issue resolves to Grade 1.
	  ○ Reduce the infusion rate by 50% for the entire remaining infusion duration.
	  ○ Medical management as per type of reaction (e.g., antihistamine, antipyretic, corticosteroids, epinephrine, bronchodilators, oxygen).
	• For the next infusion:
	  ○ Increase infusion time (reduce rate) from 60 minutes to 120 minutes.
	  ○ Premedicate the subject with an antihistamine and an antipyretic.
	  ○ Closely monitor the subject for symptoms and signs of an infusion reaction (described in [Section 6.1.2 Observation During and After Subject's Dose of Investigational Product]).
	Note: If the IP is interrupted due to an infusion reaction, such that the time from IP preparation exceeds 4 hours, then the administration must be discontinued.

Grade 3 or 4 standard infusion reactions or any reaction with features of anaphylaxis	• Stop the infusion immediately. • Institute appropriate medical management immediately based on the type of reaction (e.g., immediate treatment with intramuscular injection of epinephrine and intravenous antihistamines). • Once the subject has been stabilized, collect blood for cytokine/chemokine panel (ad hoc collection for shipment to central laboratory). • 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). Serum should be frozen if the assay cannot be performed promptly at the local laboratory.

IP: investigational product; NCI-CTCAE: National Cancer Institute Common Toxicity Criteria for Adverse Events

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 reexposure, any reaction with features of anaphylaxis should be considered potentially severe.

Reference:

La Casce AS, Castells MC, Burstein H, Meyerhardt JA Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy. UpToDate 2017. Available at: https://www.uptodate.com/contents/infusion-reactions-to-systemic-chemotherapy. Accessed 02 Oct 2018.

12.12 Eastern Cooperative Oncology Group Performance Status Scale

Grade	
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework, 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.

12.13 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	Description of abbreviations
ADA	antidrug antibody
ADL	activities of daily living
ADT	androgen deprivation therapy
AE(s)	adverse event(s)
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	Astellas Pharma Inc.
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransferases
AUC_{168h}	area under the concentration-time curve from the time of dosing to 168 hours poststart of infusion
AUC_{inf} [and %extrap]	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
AUC_{tau}	area under the concentration-time curve from the time of dosing to the start of next dosing interval
BCG	Bacillus Calmette-Guerin
BOIN	Bayesian Optimal Interval
BOR	best overall response
C	cycle
CA	competent authorities
CBC	complete blood count
CD	cluster of differentiation
CHO	Chinese hamster ovary
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CL	total clearance after intravenous dosing
C_{max}	maximum concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein-4

Abbreviations	Description of abbreviations
Ct_{rough}	concentration immediately prior to dosing at multiple dosing
CUB	complement binding factors C1r/C1s, Uegf, bone morphogenetic protein 1
CV	coefficient of variation
CVA	cerebrovascular accident
DEAS	dose limiting toxicity evaluation analysis set
DESC	Dose Escalation and Safety Committee
DILI	drug-induced liver injury
DLT(s)	dose limiting toxicity(ies)
DPD	Data Protection Directive
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
FAS	full analysis set
FFPE	Formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBc	Hepatitis B core antigen
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	"immune" confirmed progressive disease
IFNγ	interferon gamma
Ig	immunoglobin
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
irAE(s)	immune-related adverse event(s)
IRB	Institutional Review Board
iRECIST	"immune" Response Evaluation Criteria in Solid Tumors
IRR(s)	infusion-related reaction(s)

Abbreviations	Description of abbreviations
IRT	interactive response technology
ISN	international study number
iUPD	“immune” unconfirmed progressive disease
KL-6	Krebs von den Lungen-6
LA-CRF	liver abnormality case report form
LFT(s)	liver function test(s)
MAM	homologous to meprin protease, A5 antigen, receptor tyrosine phosphatase μ and Κ
mCRPC	metastatic castration resistant prostate cancer
MRI	magnetic resonance imaging
n	number of subjects
NaCl	sodium chloride
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NRP1	neuropilin-1
NSCLC	non-small cell lung cancer
PBMC(s)	peripheral blood mononuclear cell(s)
PD	progressive disease
PD-1	programmed cell death-1
PDAS	pharmacodynamic analysis set
PD-L1	programmed cell death ligand-1
PGx	pharmacogenetic
PKAS	pharmacokinetic analysis set
PR	partial response
PSA	prostate specific antigen
PT	prothrombin time
QA	quality assurance
QC	quality control
QTc	QT corrected
QTcF	QT corrected by Fridericia's Correction formula
QTLs	quality tolerance limits
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
RP2D	recommended phase 2 dose
SAE(s)	serious adverse event(s)
(S)AE	serious adverse event or adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAR(s)	serious adverse reaction(s)
SEA	serine, glutamic acid, alanine
SEMA(s)	semaphorin(s)

Abbreviations	Description of abbreviations
SOD	sum of diameters
SOP(s)	standard operating procedure(s)
SpO_2	arterial oxygen saturation
T4	thyroxine
$t_{½}$	terminal elimination half-life
TAMs	tumor associated macrophages
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
t_{last}	time of last measurable concentration
t_{max}	time of maximum concentration
TME	tumor microenvironment
TNF	tumor necrosis factor
Treg(s)	regulatory T cell(s)
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USM	urgent safety measure
V	volume of distribution after intravenous dosing
VEGF	vascular endothelial growth factor
WOCBP	woman/women of childbearing potential

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a clinical study. Note: Once a subject has received the IP or placebo, the clinical study 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 product or comparative drug (sometimes without randomization) is given to a subject, and continues until the last assessment after completing administration of the test product or comparative drug.
Postinvestigational 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 study subjects to treatment groups using chance alone to determine assignments in order to reduce bias. NOTE: Dynamic allocation is used to allocate subjects to treatment arms at differential rates using chance and prior treatment assignment.
Screening	A process of active consideration of potential subjects for enrollment in a study.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a study.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form 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.

12.14 Clinical Study Continuity

INTRODUCTION

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

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedules of Assessments [Table 1, Table 2, Table 3 and Table 4] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 7 STUDY PROCEDURES AND ASSESSMENTS] due to a crisis.

INFORMED CONSENT

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

PARTICIPANT PROCEDURES ASSESSMENT

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

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

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

Adherence to the original protocol as reflected in the Schedule of Assessment [Table 1, Table 2, Table 3 and Table 4] is expected, where plausible, in the case of a crisis. The alternate schedule below is only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate schedule change. This is to allow for continuity of receiving IP and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

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

ALTERNATIVE SCHEDULE IN RESPONSE TO A CRISIS

If the more frequent Q2W dosing schedule presents a risk to patient safety, the participant may be allowed to switch to the Q3W dosing schedule upon discussion with the Astellas medical monitor. The participant will receive the RP2D for the Q3W schedule which has been determined to be ASP1948 3000 mg. The participant will follow the Schedule of Assessment Table 2 for Dose level C. The maximum treatment duration of 2 years will also be followed for participants that switch from Q2W to Q3W dosing schedule. The Q3W dosing schedule may continue based on the benefit/risk to the participant upon discussion with the Astellas medical monitor.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol 1948-CL-0102 A Phase 1, Open-label Study of ASP1948, Targeting an Immune Modulatory Receptor, in Japanese Patients with Advanced Solid Tumors

Amendment 3 Non Substantial Date 08-SEP-2021

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Add 2-year limitation of treatment duration due to the following rationale.

- Recent in vitro study shows that ASP1948 inhibits angiogenesis. The relevance of this non-clinical finding to clinical manifestation is unclear. However, side effects of long-term treatment with typical VEGF-targeting angiogenesis inhibitors, documented in literature, serious adverse events include hemorrhage, thromboembolic events (with resultant stroke or heart attack), hypertension, impaired wound healing, reversible posterior leukoencephalopathy syndrome, proteinuria. In light of undetermined efficacy and reported AEs with ASP1948, it is reasonable to limit duration of the study.
- Immuno-oncologic mechanism of action of ASP1948 is under investigation, and AE profile associated with long term use of ASP1948 is not understood. Duration of clinical studies with Pembrolizumab is limited to 2 years and overtreatment of CPIs is associated with safety risks.

Summary of Changes

Table 14 Non Substantial Changes

Section Number	Description of Change	Brief Rationale
1.1, 1.2, 8.1	A 2-year limitation of treatment duration is added as Discontinuation of Individual Subject(s) From Study Treatment.	Recent in vitro study shows that ASP1948 inhibits angiogenesis. The relevance of this non-clinical finding to clinical manifestation is unclear. However, side effects of long-term treatment with typical VEGF-targeting angiogenesis inhibitors, documented in literature, serious adverse events

Section Number	Description of Change	Brief Rationale
		include hemorrhage, thromboembolic events (with resultant stroke or heart attack), hypertension, impaired wound healing, reversible posterior leukoencephalopathy syndrome, proteinuria. Bodnar, Richard J. "Anti-Angiogenic Drugs: Involvement in Cutaneous Side Effects and Wound-Healing Complication." Advances in wound care vol. 3,10 (2014): 635-646. doi:10.1089/wound.2013.0496 In light of undetermined efficacy and reported AEs with ASP1948, it is reasonable to limit duration of the study. In addition, immuno-oncologic mechanism of action of ASP1948 is under investigation, and AE profile associated with long term use of ASP1948 is not understood. Duration of clinical studies with Pembrolizumab is limited to 2 years and overtreatment of CPIs is associated with safety risks. Marron TU, Ryan AE, Reddy SM, et al Considerations for treatment duration in responders to immune checkpoint inhibitor Journal for ImmunoTherapy of Cancer 2021;9: e001901. doi: 10.1136/jitc-2020-001901
1.1, 6.7.3	Text is added to state that study treatment may be interrupted for up to 12 weeks for COVID-19-related illness and treatment may be resumed once COVID-19-related symptoms are no longer present.	This is to address subjects affected by the recent pandemic and to the management of subjects when they test positive for COVID-19 during the study treatment.
12.14	A Clinical Study Continuity appendix is added to the protocol. This appendix contains procedures for continuity of care during a crisis. An option for subjects to switch from Q2W to Q3W schedule is incorporated. Alternative schedules of assessments are	This appendix is added to provide acceptable alternate methods to assess safety and efficacy parameters in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster or pandemic).

Section Number	Description of Change	Brief Rationale
	provided for subjects taking part in the Q2W and Q3W schedules.	The ASP1948 3000 mg Q3W was deemed tolerable by the DESC and determined to be the RP2D and considering that it is unclear when the COVID-19 situation in Japan will resolve, an option of switching from Q2W to Q3W has been added. This modification will provide allowance for the subjects to move from the Q2W to the Q3W to address COVID-19 related safety risks.
CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL	Contact details for Sponsor's personnel, CRO's personnel, medical monitor and clinical research contact are revised.	Contact details of sponsor personnel are updated based on changes to study personnel.
1.1	The planned completion date of the study is extended to 2Q2022 (from 4Q2021).	The study period is updated to reflect the current expected duration of the study.
1.1, 6.5, 6.7.3	A criterion is added and/or clarified for treatment interruption of > 12 weeks from the end of the prior treatment cycle.	This criterion is already included in the protocol and is now added to the correct section for visibility. The clock for the 12-week timeframe is further clarified.
2.1, 2.1.1.1.1, 2.1.1.1.2, 2.1.1.1.3, 2.1.1.2.1, 2.1.1.2.2, 2.1.2.1.3	Sections 2.1 (Background), 2.1.1.1.1 (Pharmacology), 2.1.1.1.2 (Pharmacokinetics), 2.1.1.1.3 (Toxicology) and 2.1.1.2.1 (Phase 1 Results (1948-CL-0101)), 2.1.1.2.2 (Phase 1 Results (1948-CL-0102) and 2.1.2.1.3 (Increased Globulin/Increased Total Protein)) are updated with information from the latest ASP1948 Investigator's Brochure, dated Jun 2021.	This information is updated to reflect the most recent ASP1948 data available.

Section Number	Description of Change	Brief Rationale
Throughout	Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol) and update list of abbreviations and references.	To provide clarifications to the protocol and to ensure complete understanding of study procedures.