Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

SYNOPSIS

Title of Study: A Phase 1, Open-label Study to Investigate the Absorption, Metabolism, and Excretion of ^{14}C-OSI-906 in Subjects with Advanced Solid Tumors with an Optional Treatment Phase

Coordinating Investigator: [redacted] MD

Study Center: One study center in [redacted] USA

Publication Based on the Study: None.

Study Period: October 2011 to February 2013

Study Initiation Date (Date of First Enrollment): 19 October 2011

Study Completion Date (Date of Last Evaluation): 20 February 2013

Phase of Development: Phase 1

Objectives:

Primary Objective: To evaluate the pharmacokinetics, in particular the routes of excretion and extent of metabolism of OSI-906 after a single oral dose of ^{14}C-labeled OSI- 906.

Secondary Objectives: 1) To evaluate the safety of a single oral dose of ^{14}C-OSI-906 in subjects with advanced solid tumors; 2) To identify the metabolic profile of OSI-906 in plasma, urine, and feces, after a single oral dose of ^{14}C-labeled OSI-906; 3) To assess the safety of repeat-dose oral administration of study drug in subjects with advanced solid tumors.

Methodology:

Part A: This was an open-label, phase 1 study to investigate the absorption, metabolism, and excretion of ^{14}C-OSI-906 in subjects with advanced solid tumors consisting of 2 parts (A and B). Part A subjects were screened for up to 21 days prior to study drug administration. Eligible subjects were admitted to the clinical research unit on day -1 and remained confined to the unit until post-dosing discharge criteria were met. On day 1, subjects consumed a standardized meal within 30 minutes prior to dosing. Subjects received a single oral dose of 150 mg in 60 mL consisting of ~1 mg (100 μCi) ^{14}C-OSI-906 and ~149 mg unlabeled OSI-906. The median $t_{1/2}$ of OSI-906 after a single 150 mg dose was found to be 2.1 to 4.6 hours. Therefore, a maximum confinement period of up to 10 days was considered to be sufficient to evaluate the routes of excretion and extent of metabolism. Whole blood, plasma, and urine samples for analysis of ^{14}C- radioactivity, OSI-906 and potential metabolites were collected until post-dosing discharge criteria were met (or up to 216 hours post-dosing if necessary). Fecal samples were collected for analysis of ^{14}C-radioactivity and potential metabolites. Emesis samples (if applicable) were collected for ^{14}C-radioactivity only.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

Subjects were discharged if: 1) there were no medical reasons to keep the subject in the clinic as assessed by the principal investigator, and 2) two consecutive blood samples contain less than 2 times background radioactivity, and 3) a. sufficient recovery of administered radioactivity had been achieved (approximately 95% or more of the administered dose), OR b. radioactivity in urine and feces was ≤ 1% total dose in each of 2 consecutive samples. In the event ^{14}C-radioactivity counts indicated that radioactivity in urine or feces was above these limits or recovery of radioactivity was insufficient, the subjects was required to stay in the clinical unit until the criteria outlined above had been met for discharge or until day 10 if the criteria had not been met sooner. Blood, plasma, urine, feces and emesis (if applicable) samples for absorption, metabolism and excretion assessments were collected at scheduled intervals. Safety was assessed by adverse events (AE) reporting, vital signs, electrocardiogram (ECG), physical examinations, and lab evaluations. Subjects not continuing into the optional treatment phase (Part B) completed a 30 day post-treatment visit.

Part B: Once part A had completed, the subjects could elect to continue participation in Part B. Subjects received OSI-906 (non-radiolabeled) twice daily by mouth. The start of Part B was to be ≤ 10 days after completion of Part A. Subjects were seen for scheduled study visits every 21 days. This time period was defined as a treatment period (TP). All assessments were performed prior to dosing on day 1 of each TP.

- For the first 2 TPs (approximately 42 days), subjects had safety labs drawn on a weekly basis.
- Beginning with TP 3, assessments were to be performed at each TP or approximately every 21 days.
- After the subject had been on study drug for 5 TPs (approximately 85 days), visits may be reduced to every 42 days until early discontinuation (ED) or end of study (EOS).

All subjects had a 30-day post-treatment visit.

Number of Patients (Planned, Enrolled and Analyzed):

Planned: Six subjects

Enrolled: Five subjects

Analyzed in Part A: Five subjects

Analyzed in Part B: Five subjects

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

Diagnosis and Main Criteria for Inclusion:

Subjects with advanced solid tumors were selected for this study.

Inclusion Criteria - Part A: Subjects were considered for inclusion into the study if they met the following eligibility criteria:

1. Institutional Review Board approved written informed consent and privacy language as per national regulations had been obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

2. The subject had histologically or cytologically confirmed diagnosis of advanced solid tumor (measurable or non-measurable disease) for which no conventional therapy is available.

3. The subject was male or female age ≥ 18 years.

4. The subject had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2.

5. The subject had a predicted life expectancy ≥ 12 weeks.

6. The subject had a fasting glucose ≤ 125 mg/dL (7 mmol/L) at Screening, day -1 and pre-dose day 1.

7. The subject had adequate organ function defined by the following laboratory parameters:

   a. absolute neutrophil count ≥ 1.5 x 10^9/L

   b. platelet count ≥ 100 x 10^9/L

   c. total bilirubin ≤ 1.5 x upper limit of normal (ULN)

   d. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN, or ≤ 5 x ULN if subject had documented liver metastases

   e. serum creatinine ≤ 1.5 x ULN

   f. potassium, calcium, and magnesium within normal limits or determined by the investigator to be not clinically significant.

8. If male, the subject was surgically sterile (with documentation provided by a healthcare professional), or was using a medically acceptable method to prevent pregnancy and agreed to continue using this method while participating in the study and for 90 days after the last dose of study medication.

9. If female, the subject was surgically sterile or status post-hysterectomy (at least 1 month prior to Screening with documentation provided by a healthcare professional), post-menopausal (defined as at least 2 years without menses at screening and a confirmatory follicle stimulating hormone level of ≥ 40 U/L at screening), or was using 2 forms of medically acceptable methods of birth control, 1 of which was a barrier method, to prevent

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

pregnancy and agrees to continue using this method from screening until 90 days after the last dose of study medication.

10. Female subject of child bearing potential had a negative pregnancy test at Screening and day -1.

Exclusion Criteria – Part A:

Subjects were excluded from participation if any of the following applied:

1. The subject had Type 1 or Type 2 diabetes mellitus that required insulinotropic or insulin therapy.

2. The subject had a history of poorly controlled gastrointestinal disorder (s) that could affect the absorption or metabolism of study drug (e.g., > Grade 1 diarrhea or > Grade 1 constipation 1 week prior dosing, Crohn's disease, ulcerative colitis, etc.).

3. The subject had used IGF-1R inhibitor therapy in the last 6 months.

4. The subject had hepatocellular carcinoma.

5. The subject had used a CYP 1A2 inhibitor or inducer within 14 days prior to day 1.

6. The subject had used drugs with a risk of causing QTc interval prolongation and Torsade de Pointes within 14 days prior to enrollment.

7. The subject had a history (within last 6 months) of significant cardiovascular disease, including:

a. second/third degree heart block

b. clinically significant ischemic heart disease

c. mean QTcF interval of > 450 msec at Screening and at pre-dose on day 1

d. poorly controlled hypertension

e. Superior Vena Cava Syndrome

f. congestive heart failure of New York Heart Association Class II or worse.

8. The subject had a history (within the last 6 months) of significant arrhythmia disease, unless the disease was well-controlled with medication per the principal investigator's clinical judgment. Significant arrhythmia disease included:

a. arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) that was symptomatic or required treatment (≥ Grade 3)

b. left bundle branch block

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

c. asymptomatic sustained ventricular tachycardia

d. atrial fibrillation not controlled by medication.

9. The subject had surgery ≤ 3 weeks prior to day 1.

10. The subject had radiation ≤ 3 weeks prior to day 1.

11. The subject had chemotherapy ≤ 3 weeks prior to day 1.

12. The subject had participated in a radiolabeled study in the last 12 months.

13. The subject had a history of cerebrovascular accident within 6 months prior to day 1 or that resulted in ongoing neurologic instability.

14. The subject had an active infection or serious underlying medical condition (including any type of active seizure disorder within 12 months prior to day 1) that would impair the ability of the subject to receive study drug.

15. The subject had participated in any interventional clinical study within 21 days or had been treated with any investigational drugs within 30 days or 5 half lives whichever was longer, prior to the initiation of Screening.

16. The subject had a history of any psychiatric condition that might impair the subject's ability to understand or to comply with the requirements of the study or to provide informed consent.

17. The subject had symptomatic brain metastases that were not stable, required steroids, or that had required radiation and/or other related treatment, (i.e., anti-epileptic medication) within 28 days prior to day 1.

18. The subject had a history of allergic reactions attributed to compounds of similar chemical or biologic composition to the study drug.

Inclusion and Exclusion Criteria - Part B: Subjects were eligible for the study if they has participated in Part A and continued to meet Inclusion Criteria 6 and 7, and not meet Exclusion Criteria 4. Subjects in Part B of the study could continue to receive study drug for as long as the Investigator felt it was appropriate. Subjects were to be discontinued from the study in case of disease progression, mean QTcF > 501 msec, failure to recover from hematological and/or non-hematological toxicity, despite a dosing interruption of up to 14 days (recovery defined as ≤ Grade 2 Common Terminology Criteria for Adverse Events [CTCAE] v4.02), increased liver function tests, withdrawal of consent, significant protocol violation (e.g., subject took prohibited medication and/or demonstrated lack of cooperation in following protocol specified procedures/instructions), or investigator or sponsor felt it was the subject's best interest.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

Test Product, Dose and Mode of Administration, Batch Numbers:

Part A:

OSI-906 and ^{14}C-OSI-906 60 mL solution, which comprised 150 mg consisting of ~1 mg (100 μCi) ^{14}C-OSI-906 and ~149 mg unlabeled OSI-906.

Single dose, oral solution

Part B:

OSI-906 25, 100, or 150 mg tablets given twice daily (BID), orally

Duration of Treatment (or Duration of Study, if applicable):

All subjects were treated until disease progression or unacceptable study drug toxicity.

Criteria for Evaluation:

Radioactivity

- Radioactivity in whole blood

  AUC_{inf} - 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 (C_{last})

  C_{max} - Maximum concentration

  t_{max} - Time of the maximum concentration

  $t_{1/2}$ - Terminal elimination half-life

  CL/F - Apparent total systemic clearance after single or multiple extra-vascular dosing

  V_z/F - Apparent volume of distribution during the terminal elimination phase after single extra-vascular dosing

- Radioactivity in plasma

  AUC_{inf}, AUC_{last}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F

- In emesis (if applicable)
- Radioactivity ratio blood/plasma
- Excretion ratio and cumulative excretion of radioactivity in urine
- Excretion ratio and cumulative excretion of radioactivity in feces

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

Pharmacokinetics

- For OSI-906 in plasma

  AUC_{inf}, AUC_{last}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F

- For OSI-906 in urine

  Cumulative amount of drug excreted in urine (Ae_{last}), CLR and % fraction of drug excreted in urine ($Ae_{last\%}$)

Metabolic Profile

- Profiling of possible metabolites in plasma, urine and feces

Safety and tolerability assessments:

- Adverse event reporting
- Clinical laboratory evaluations
- 12-lead ECGs
- Vital sign measurements (oral temperature, respiration rate, pulse and supine blood pressure)

Statistical Methods:

Part A:

Radioactivity in Blood and Plasma: pharmacokinetic parameters were computed from plasma concentrations of OSI-906 and possible metabolites and were interpreted in relation to pharmacokinetic parameters calculated from plasma radioactivity. To provide a measure of OSI-906 distribution between blood cellular components and plasma, the ratio of radioactivity in blood/plasma were presented. Descriptive statistics were used to summarize the concentrations, radioactivity and pharmacokinetic parameters. Appropriate graphic techniques were used to illustrate the data.

Radioactivity in Urine and Feces: pharmacokinetic parameters were computed from urine concentrations of OSI-906 and possible metabolites and were interpreted in relation to pharmacokinetic parameters calculated from urine radioactivity. Excretion rate, cumulative excretion of radioactivity and percent of dose excreted in urine and feces were determined and tabulated. Descriptive statistics were used to summarize the concentrations, radioactivity and pharmacokinetic parameters. Appropriate graphic techniques were used to illustrate the data.

Part B:

Safety data were summarized in individual subject listings.

Part B safety reporting cut-off date occurred when all subjects had discontinued study drug or the last remaining subject(s) on study drug had at least 6 months of study drug exposure.

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

Summary of Results/Conclusions:

Doses of OSI-906 ranged from 148 to 156 mg (105 to 107 µCi), and were close to the target dose of 150 mg (100 µCi). Maximum mean concentrations of study drug-derived radioactivity in blood and plasma were observed at approximately 3 hours post-dose, with mean values of 1454 and 1936 ng_equivalents/g, respectively. Maximum plasma and blood radioactivity concentrations in individual subjects were observed from 1 to 4 hours and 2 to 4 hours post-dose, respectively. Levels of radioactivity fell below the limit of quantitation for all subjects by 24 hours post-dose in blood and 48 hours post-dose in plasma. The plasma and blood pharmacokinetics of ^{14}C-OSI-906 observed in this study were consistent with that of non-radiolabeled OSI-906 from other clinical studies of OSI-906.

The overall mean recovery of radioactivity in urine, feces, and toilet tissue samples was 81.8% over the 240-hour study, with recovery in individual subjects ranging from 86.1% to 93.3% for 4 of the 5 subjects, and 46.6% in the remaining subject. A mean of 76.3% of the dose was excreted in feces with a mean of 5.44% excreted in urine through the last collection interval. Most of the administered radioactivity was recovered in the first 192 hours post-dose (77.5%).

Pharmacokinetic Results:

Five subjects each received a single, target 150-mg (approximately 100-µCi) oral dose of ^{14}C-OSI-906. The concentrations of radioactivity in blood, plasma, urine, feces, pleural fluid, and IC pad samples, and the percent of radioactive dose in urine, feces, toilet tissue, emesis, and IC pad samples were determined.

- Maximum mean concentrations of study drug-derived radioactivity in blood and plasma were observed at approximately 3 hours post-dose, with mean values of 1454 and 1936 ng_equivalents/g, respectively.
- Mean blood-to-plasma concentration ratios ranged from 0.724 to 0.807 through 12 hours post-dose.
- Greater than 80% of the dose was recovered in feces for 4 of the 5 subjects, and 41.7% of the dose was recovered from the remaining subject. Overall, a mean of 76.3% of the dose was excreted in feces (mean total amount 115000 µg_equivalents) and 5.44% was excreted in urine (8200 µg_equivalents) through the last collection interval.
- Most of the administered radioactivity was recovered in the first 192 hours post-dose (77.5%). The overall mean recovery of radioactivity in urine, feces, and toilet tissue samples was 81.8%. Recovery in individual subjects ranged from 86.1% to 93.3% for 4 of the 5 subjects, and was 46.6% in the remaining subject.

Safety Results:

The administration of OSI-906 as a single dose or in doses up to 150 mg (BID) were tolerated in this population of cancer patients with advanced solid tumors. There were no discernible trends toward hyperglycemia, renal failure, increases in liver function tests, or QTc prolongation. There were 2 deaths in Part B of the study: the cause of death for patient [redacted] was listed as [redacted], and was considered to be attributable

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Linsitinib (OSI-906, ASP7487)		

to disease progression and not related to study medication; the cause of death for patient [redacted] was listed as [redacted] and was considered to be attributable to disease progression and not related to study medication.

CONCLUSIONS:

Overall, these results suggest that OSI-906 was predominantly excreted through the feces and minimally excreted in the urine, and OSI-906 is effectively eliminated within 10 days following a single 150 mg dose. In Part B, these 5 subjects completed between 1 and 3 treatment cycles of OSI-906 before study discontinuation. No subject was permanently discontinued from study treatment as a result of an AE, and no new safety signals were identified.

Date of Report: 23 January 2014

Table 1 Patient Disposition

Parameter	Category	Part A n = 5	Part B n = 5
Treatment Discontinuation	Yes	0	5 (100.0%)
	No	5 (100.0%)	0
	Completed	5 (100.0%)	0
Primary Reason for Discontinuation [1]	Progressive Disease	0	5 (100.0%)

[1] Only the primary reason for discontinuation was collected
Source: Table 12.1.1.2

Table 2 Demographic Characteristics

Characteristic	Part A n = 5	Part B n = 5
Sex		
Male	3 (60.0%)	3 (60.0%)
Female	2 (40.0%)	2 (40.0%)
Race		
White	5 (100.0%)	5 (100.0%)
Age (years)		
Mean (SD)	68.0 (9.2)	68.0 (9.2)
Min – Max	56 – 79	56 - 79
Weight (kg)		
Mean (SD)	71.68 (23.73)	71.68 (23.73)
Min – Max	53.5 - 109.2	53.5 - 109.2
Height (cm)		
Mean (SD)	165.2 (10.7)	165.2 (10.7)
Min – Max	156 – 180	156 - 180
BMI (kg/m^2)		
Mean (SD)	25.92 (5.03)	25.92 (5.03)
Min – Max	21.3 - 34.2	21.3 - 34.2
ECOG Performance Status		
Grade 0	1 (20.0%)	1 (20.0%)
Grade 1	3 (60.0%)	3 (60.0%)
Grade 2	1 (20.0%)	1 (20.0%)

BMI: body mass index, ECOG: Eastern Cooperative Oncology Group
Source: Table 12.1.2.1 and Table 12.1.2.2

Table 3 Summary of Pharmacokinetic Parameters for ^{14}C-Radioactivity in Whole Blood After a Single 150-mg (100 µCi) Oral Dose of ^{14}C-OSI-906 to Subjects

	AUC_{inf} (ng eq·h/mL)	AUC_{last} (ng eq·h/mL)	C_{max} (ng eq/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
n	3	5	5	5	3	3	3
Mean	10373	7612	1454	3.000	2.879	15.12	62.42
SD	NA	3302	734.1	0.7071	NA	NA	NA
%CV	NA	43.4	50.5	NA	NA	NA	NA
Minimum	7884	3859	821	2.00	2.54	11.3	44.5
Median	9983	7420	1200	3.000	2.728	15.03	69.63
Maximum	13253	12493	2680	4.00	3.37	19.0	73.1
Geometric mean	NA	7043	1332	NA	NA	NA	NA

CV: coefficient of variation, NA: not applicable
Source: Table 12.4.3.1

Table 4 Summary of Pharmacokinetic Parameters for ^{14}C-Radioactivity in Plasma After a Single 150-mg (100 µCi) Oral Dose of ^{14}C-OSI-906 to Subjects

Statistic	AUC_{inf} (ng eq·h/mL)	AUC_{last} (ng eq·h/mL)	C_{max} (ng eq/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
n	3	5	5	5	3	3	3
Mean	15592	11483	1936	2.603	4.164	0.009970	0.05761
SD	NA	5477	1073	1.134	NA	NA	NA
%CV	NA	47.7	55.4	NA	NA	NA	NA
Minimum	12192	5025	959	1.02	2.52	0.00774	0.0447
Median	15198	11509	1810	3.000	4.511	0.009870	0.05036
Maximum	19388	18843	3640	4.00	5.46	0.0123	0.0778
Geometric mean	NA	10362	1722	NA	NA	NA	NA

CV: coefficient of variation, NA: not applicable
Source: Table 12.4.3.2

Table 5 Cumulative Percent of Radioactive Dose Recovered in Urine, Feces, and Toilet Tissue After Administration of a Single 150-mg (100 µCi) Oral Dose of ^{14}C-OSI-906 to Subjects

Statistic	Ae urine (%)	Ae feces (%)	Ae toilet tissue (%)	Ae total (%)
n	5	5	2	5
Mean	5.44	76.2	0.183	81.7
SD	0.677	19.5	NA	19.8
Minimum	4.60	41.7	0.0291	46.6
Median	5.46	84.1	0.183	89.3
Maximum	6.47	87.6	0.337	93.3

Values cumulative from 0 – 240 hours post-dose.

Ae%: percent of radioactive dose recovered, NA: not applicable

Source: Attachment 2

Table 6 Part B: Treatment-Emergent Adverse Events - Safety Analysis Set

System Organ Class (MedDRA v12.0) Preferred Term	**All AEs** **n = 5**	**Drug-Related** **n = 5**
Overall	5 (100.0)	4 (80.0)
Blood and lymphatic system disorders	2 (40.0)	2 (40.0)
Anaemia	1 (20.0)	1 (20.0)
Lymphopenia	1 (20.0)	1 (20.0)
Cardiac disorders	2 (40.0)	0
Atrial fibrillation	1 (20.0)	0
Cardiac failure congestive	1 (20.0)	0
Cardiac tamponade	1 (20.0)	0
Cardio-respiratory arrest	1 (20.0)	0
Pericardial effusion	1 (20.0)	0
Ear and labyrinth disorders	1 (20.0)	1 (20.0)
Ear congestion	1 (20.0)	1 (20.0)
Gastrointestinal disorders	4 (80.0)	3 (60.0)
Abdominal distension	1 (20.0)	0
Abdominal pain	1 (20.0)	0
Ascites	1 (20.0)	0
Constipation	2 (40.0)	0
Diarrhoea	1 (20.0)	1 (20.0)
Dry mouth	1 (20.0)	0
Nausea	2 (40.0)	2 (40.0)
Upper gastrointestinal haemorrhage	1 (20.0)	0
Vomiting	1 (20.0)	0
General disorders and administration site conditions	3 (60.0)	3 (60.0)
Fatigue	3 (60.0)	3 (60.0)
Pitting oedema	1 (20.0)	0
Infections and infestations	1 (20.0)	0
Urinary tract infection bacterial	1 (20.0)	0
Injury, poisoning and procedural complications	2 (40.0)	0
Excoriation	0	0
Procedural pain	1 (20.0)	0
Seroma	1 (20.0)	0
Skin injury	0	0
Investigations	2 (40.0)	1 (20.0)
Blood creatinine increased	1 (20.0)	0
Liver function test abnormal	1 (20.0)	1 (20.0)
Weight decreased	1 (20.0)	1 (20.0)
Metabolism and nutrition disorders	2 (40.0)	2 (40.0)
Anorexia	2 (40.0)	2 (40.0)
Cachexia	1 (20.0)	0
Dehydration	1 (20.0)	1 (20.0)
Failure to thrive	1 (20.0)	1 (20.0)
Hypoalbuminaemia	2 (40.0)	0
Malnutrition	1 (20.0)	0

Table continued on next page

Table 6 continued

System Organ Class (MedDRA v12.0) Preferred Term	**All AEs** **n = 5**	**Drug-Related** **n = 5**
Musculoskeletal and connective tissue disorders	2 (40.0)	0
Back pain	1 (20.0)	0
Muscular weakness	1 (20.0)	0
Nervous system disorders	3 (60.0)	3 (60.0)
Dizziness	1 (20.0)	1 (20.0)
Dysgeusia	2 (40.0)	1 (20.0)
Headache	1 (20.0)	1 (20.0)
Lethargy	1 (20.0)	1 (20.0)
Respiratory, thoracic and mediastinal disorders	3 (60.0)	1 (20.0)
Dyspnoea	1 (20.0)	0
Dyspnoea exertional	2 (40.0)	1 (20.0)
Hypoxia	2 (40.0)	0
Wheezing	1 (20.0)	0
Skin and subcutaneous tissue disorders	1 (20.0)	1 (20.0)
Pruritus	1 (20.0)	1 (20.0)
Vascular disorders	2 (40.0)	0
Hypotension	2 (40.0)	0

Number of subjects (n) and percentage of subjects (%) are shown
Sorting order: alphabetical by system organ class and preferred term.
AEs: Adverse events

Source: Table 12.6.1.2 and Table 12.6.1.3