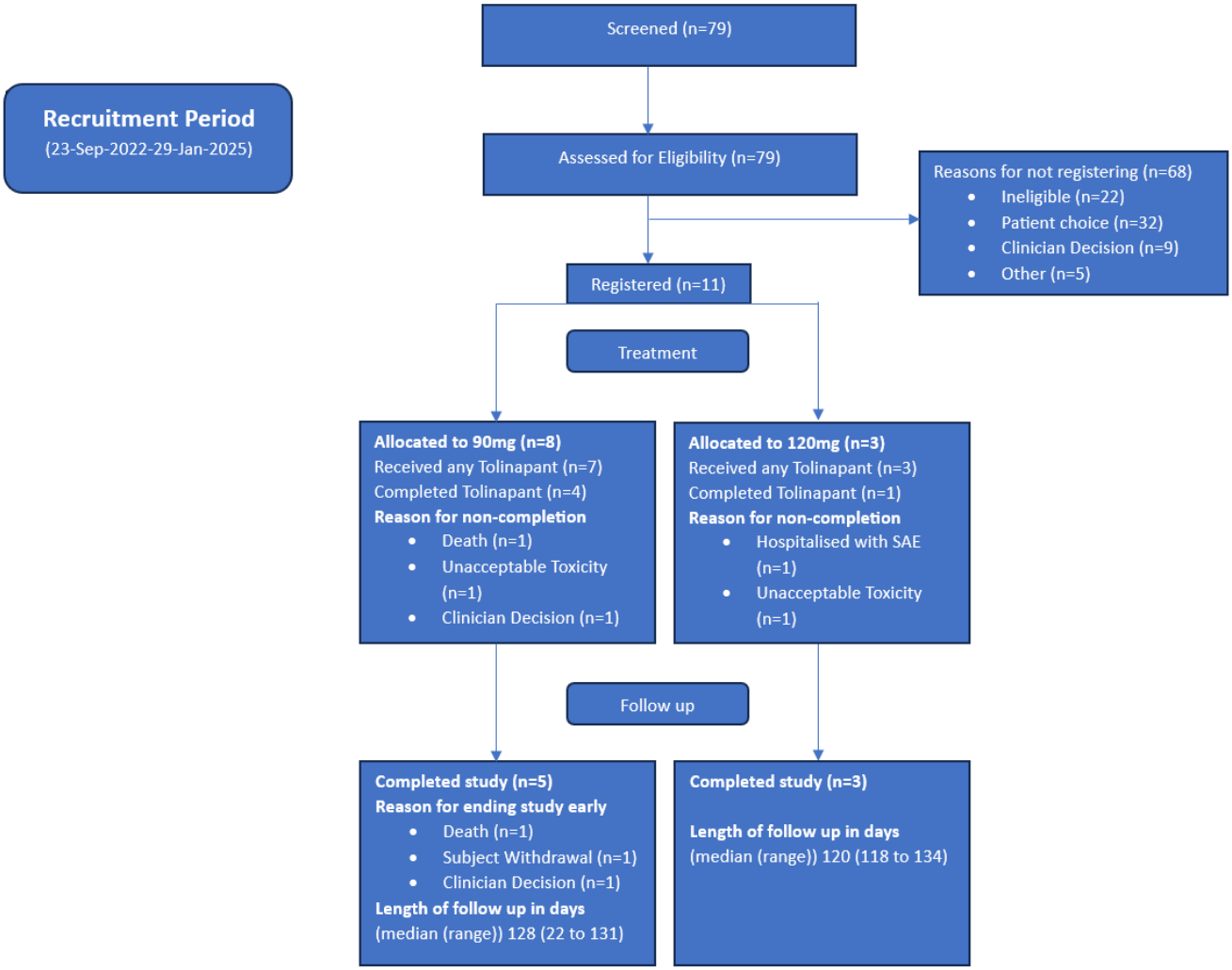
# CRAIN Results Summary

## Participant Flow



## Baseline Characteristics

| | 90mg (n=8) | 120mg (n=3) |
|---|---|---|
| **Age at consent (years)** | | |
| Median (Quartiles) | 47.5 (44.0 to 54.0) | 40.0 (35.0 to 61.0) |
| **Ethnicity** | | |
| Asian/Asian British- Chinese | 1 (12.5%) | 0 (0.0%) |
| White- Scottish/English/Welsh/Northern Irish/British | 5 (62.5%) | 3 (100%) |
| Not given | 2 (25.0%) | 0 (0.0%) |
| **ECOG Status** | | |
| 0 = Fully active | 7 (87.5%) | 3 (100%) |
| 1 = Restricted in physically strenuous activity but ambulatory | 1 (12.5%) | 0 (0.0%) |
| **Type of Cervical Cancer** | | |
| Adenocarcinoma | 5 (62.5%) | 0 (0.0%) |
| Squamous cell carcinoma | 3 (37.5%) | 3 (100%) |
| **FIGO stage** | | |
| IB2 | 3 (37.5%) | 0 (0.0%) |
| IIA1 | 0 (0.0%) | 1 (33.3%) |
| IIB | 4 (50.0%) | 1 (33.3%) |
| IIIC | 1 (12.5%) | 1 (33.3%) |
| **Fecal urgency (RT-ARD score)** | | |
| 1 = Ability to defer defecation more than 15 minutes | 8 (100%) | 2 (66.7%) |
| Not collected in error | 0 (0.0%) | 1 (33.3%) |
| **Metastases Present?** | | |
| Yes | 0 (0.0%) | 0 (0.0%) |
| No | 8 (100%) | 3 (100%) |
| **Lymph Nodes present in pelvis?** | | |
| Yes | 0 (0.0%) | 1 (33.3%) |
| No | 8 (100%) | 2 (66.7%) |
| **Number of Target lesions** | | |
| Median (Quartiles) | 1 (1 to 1) | 1 (1 to 1) |
| **Sum of Target lesions (mm)** | | |
| Median (Quartiles) | 42 (20 to 48) | 25 (24 to 45) |

# Outcome Measures

| | 90mg (n=7) | 120mg (n=3) |
|---|---|---|
| Number of Patients included | 7 | 3 |
| Number of Patients who experienced a DLT - n (%)[1] | 0 (0.0%) | 2 (66.7%) |
| Number of DLT events[2] | 0 | 5 |
| Number of patients experiencing each type of DLT - n (%)[3] [no. of events] | | |
| Grade 4 neutropenia[4] | 0 (0.0%) [0] | 0 (0.0%) [0] |
| Grade 3 or 4 febrile neutropenia[4] | 0 (0.0%) [0] | 0 (0.0%) [0] |
| Grade 3 or 4 neutropenia[4] | 0 (0.0%) [0] | 0 (0.0%) [0] |
| Grade 3 or 4 thrombocytopenia[4] | 0 (0.0%) [0] | 0 (0.0%) [0] |
| Other Grade 3+ AE[4] | 0 (0.0%) [0] | 2 (100%) [5] |
| Alanine aminotransferase increased (Grade 3, probably related) | 0 (0.0%) [0] | 1 (50.0%) [1] |
| Generalised tonic-clonic seizure (Grade 3, probably related) | 0 (0.0%) [0] | 1 (50.0%) [1] |
| Haemorrhage intracranial (Grade 4, probably related) | 0 (0.0%) [0] | 1 (50.0%) [1] |
| Hemianopia (Grade 3, probably related) | 0 (0.0%) [0] | 1 (50.0%) [1] |
| Transverse sinus thrombosis (Grade 4, probably related) | 0 (0.0%) [0] | 1 (50.0%) [1] |
| Death[4] | 0 (0.0%) [0] | 0 (0.0%) [0] |

[1] Denominator is the number of patients.

[2] The TiTE CRM model is based on the number of patients experiencing a DLT, not the no. of events that meet the criteria.

[3] Denominator is the number of patients who experienced a DLT.

[4] Only a DLT if clinically defined as definitely or probably related to Tolinapant. See full DLT criteria for more details on requirements to be defined as a DLT.

**According to the model, the recommended phase 2 dose level is 3 (120mg). However, the overall decision by the Safety Review Committee, Chief Investigator, and the Trial Management Group was to select 90mg as the recommended phase 2 dose.**

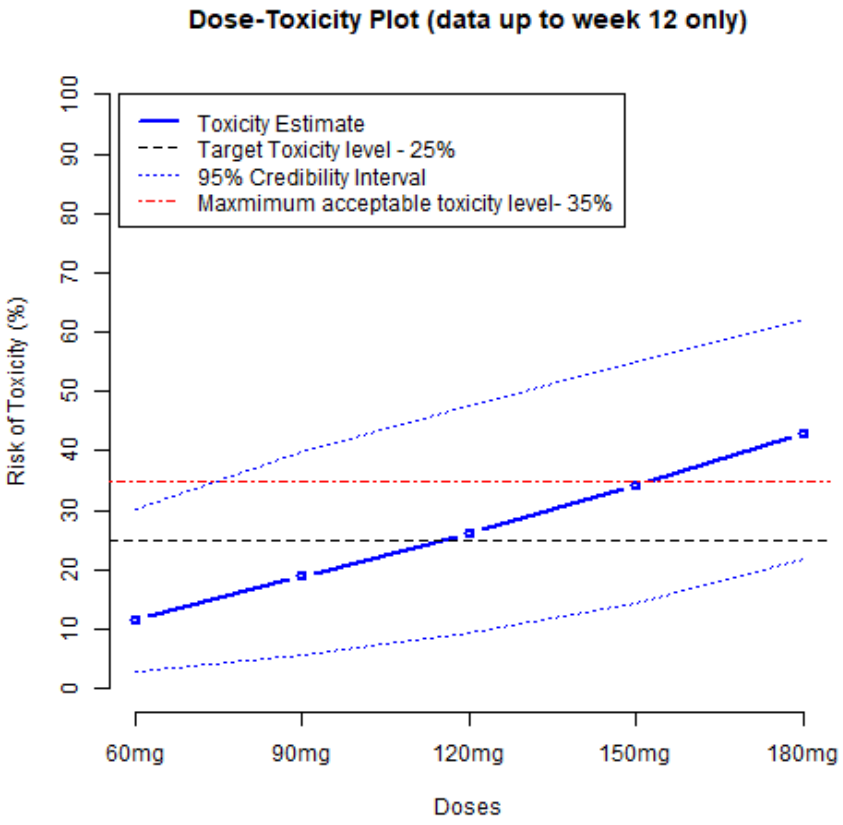
| | Dose level | | | | |
|---|---|---|---|---|---|
| | 60mg (n=0) | 90mg (n=7) | 120mg (n=3) | 150mg (n=0) | 180mg (n=0) |
| Number of patients included in the model | 0 | 7 | **3** | 0 | 0 |
| Number of full patient assessment equivalents[1] | 0 | 5.64 | **3** | 0 | 0 |
| Number of patients with DLT | N/A | 0 | **2** | N/A | N/A |
| Estimated DLT rate[2] | 11.7% | 18.9% | **26.1%** | 34.1% | 43.1% |
| (95% Credible equal tail interval) | (2.8 to 30.1) | (5.6 to 39.9) | **(9.2 to 47.7)** | (14.4 to 55.0) | (21.7 to 62.1) |
| Target dose probability[3] | 13.3% | 31.1% | **36.9%** | 26.7% | 10.3% |
| Probability of being too toxic[4] | 0.9% | 6.5% | **20.7%** | 46.6% | 76.6% |

*1 A full patient assessment equivalent is defined as 12 weeks (84 days). Once a patient has reached day 84 or experienced a DLT they count as one full assessment. Otherwise, the equivalent is calculated as number of days since treatment start/84 for each patient. This figure is the sum of all patients who have received treatment.*

*2 Estimated using the TiTE-CRM model – all information for each dose is used to model toxicity for all levels.*

*3 Probability the dose lies within the target toxicity level (20-30%), estimated using the model.*

*4 Probability the dose is too toxic, i.e. greater than 35%.*


Dose-Toxicity Plot (data up to week 12 only)
Toxicity Estimate
Target Toxicity level - 25%
95% Credibility Interval
Maxmimum acceptable toxicity level- 35%
Risk of Toxicity (%)
0
10
20
30
40
50
60
70
80
90
100
60mg
90mg
120mg
150mg
180mg
Doses

# Adverse Events

**Overall toxicity summary by SOC and PT term – Evaluable population**

| | Dose Level | | |
|---|---|---|---|
| | **90mg (n=7)** | **120mg (n=3)** | **Total (n=10)** |
| **Number of patients that experienced at least one AE - n (%) [no. of events]** | **7 (100%) [147]** | **3 (100%) [71]** | **10 (100%) [218]** |
| **Summary of AEs - n (%)[1] [no. of events]** | | | |
| **Blood and lymphatic system disorders** | **2 (28.6%) [4]** | **1 (33.3%) [1]** | **3 (30.0%) [5]** |
| Anaemia | 2 (28.6%) [3] | 1 (33.3%) [1] | 3 (30.0%) [4] |
| Neutropenia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Cardiac disorders** | **1 (14.3%) [1]** | **0 (0.0%) [0]** | **1 (10.0%) [1]** |
| Sinus Tachycardia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Ear and labyrinth disorders** | **1 (14.3%) [3]** | **1 (33.3%) [2]** | **2 (20.0%) [5]** |
| Ear Pain | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Hypoacusis | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Tinnitus | 1 (14.3%) [2] | 1 (33.3%) [1] | 2 (20.0%) [3] |
| **Endocrine disorders** | **0 (0.0%) [0]** | **1 (33.3%) [1]** | **1 (10.0%) [1]** |
| Diabetes Insipidus | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| **Eye disorders** | **0 (0.0%) [0]** | **1 (33.3%) [1]** | **1 (10.0%) [1]** |
| Papilloedema | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| **Gastrointestinal disorders** | **7 (100%) [42]** | **3 (100.0%) [13]** | **10 (100%) [55]** |
| Abdominal Pain | 3 (42.9%) [5] | 1 (33.3%) [1] | 4 (40.0%) [6] |
| Abdominal Pain Lower | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Constipation | 2 (28.6%) [3] | 1 (33.3%) [1] | 3 (30.0%) [4] |
| Diarrhoea | 6 (85.7%) [11] | 3 (100.0%) [6] | 9 (90.0%) [17] |
| Dry Mouth | 1 (14.3%) [1] | 1 (33.3%) [1] | 2 (20.0%) [2] |
| Dyspepsia | 4 (57.1%) [6] | 0 (0.0%) [0] | 4 (40.0%) [6] |
| Flatulence | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Mouth Ulceration | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Nausea | 4 (57.1%) [7] | 2 (66.7%) [3] | 6 (60.0%) [10] |
| Small Intestinal Obstruction | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Tongue Ulceration | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Vomiting | 3 (42.9%) [5] | 0 (0.0%) [0] | 3 (30.0%) [5] |
| **General disorders and administration site conditions** | **5 (71.4%) [9]** | **3 (100.0%) [4]** | **8 (80.0%) [13]** |
| Fatigue | 5 (71.4%) [7] | 3 (100.0%) [3] | 8 (80.0%) [10] |
| Pyrexia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Thirst | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Vaccination Site Reaction | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Immune system disorders** | **1 (14.3%) [1]** | **0 (0.0%) [0]** | **1 (10.0%) [1]** |
| Seasonal Allergy | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Infections and infestations** | **2 (28.6%) [4]** | **1 (33.3%) [2]** | **3 (30.0%) [6]** |
| Pneumonia | 1 (14.3%) [1] | 1 (33.3%) [1] | 2 (20.0%) [2] |
| Urinary Tract Infection | 1 (14.3%) [2] | 1 (33.3%) [1] | 2 (20.0%) [3] |
| Vaginal Infection | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Injury, poisoning and procedural complications** | **1 (14.3%) [1]** | **0 (0.0%) [0]** | **1 (10.0%) [1]** |
| Procedural Vomiting | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Investigations** | **7 (100%) [33]** | **2 (66.7%) [25]** | **9 (90.0%) [58]** |
| Alanine Aminotransferase Increased | 4 (57.1%) [6] | 1 (33.3%) [6] | 5 (50.0%) [12] |
| Amylase Increased | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Aspartate Aminotransferase Increased | 2 (28.6%) [2] | 1 (33.3%) [1] | 3 (30.0%) [3] |
| Blood Alkaline Phosphatase Increased | 1 (14.3%) [2] | 0 (0.0%) [0] | 1 (10.0%) [2] |
| Blood Calcium Decreased | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Blood Magnesium Decreased | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |

| | Dose Level | | |
|---|---|---|---|
| | 90mg (n=7) | 120mg (n=3) | Total (n=10) |
| Blood Urea Increased | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Gamma-Glutamyl transferase Increased | 1 (14.3%) [2] | 1 (33.3%) [1] | 2 (20.0%) [3] |
| Haemoglobin Decreased | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Lipase Increased | 4 (57.1%) [9] | 2 (66.7%) [3] | 6 (60.0%) [12] |
| Lymphocyte Count Decreased | 1 (14.3%) [2] | 2 (66.7%) [7] | 3 (30.0%) [9] |
| Neutrophil Count Decreased | 2 (28.6%) [2] | 0 (0.0%) [0] | 2 (20.0%) [2] |
| Platelet Count Decreased | 1 (14.3%) [2] | 2 (66.7%) [2] | 3 (30.0%) [4] |
| Vitamin D Decreased | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Weight Decreased | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| White Blood Cell Count Decreased | 1 (14.3%) [2] | 1 (33.3%) [2] | 2 (20.0%) [4] |
| **Metabolism and nutrition disorders** | **7 (100%) [16]** | **0 (0.0%) [0]** | **7 (70.0%) [16]** |
| Decreased Appetite | 3 (42.9%) [5] | 0 (0.0%) [0] | 3 (30.0%) [5] |
| Hyperglycaemia | 1 (14.3%) [2] | 0 (0.0%) [0] | 1 (10.0%) [2] |
| Hypoalbuminaemia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Hypomagnesaemia | 4 (57.1%) [8] | 0 (0.0%) [0] | 4 (40.0%) [8] |
| **Musculoskeletal and connective tissue disorders** | **1 (14.3%) [1]** | **2 (66.7%) [5]** | **3 (30.0%) [6]** |
| Arthralgia | 1 (14.3%) [1] | 1 (33.3%) [1] | 2 (20.0%) [2] |
| Muscle Spasms | 0 (0.0%) [0] | 1 (33.3%) [4] | 1 (10.0%) [4] |
| **Nervous system disorders** | **5 (71.4%) [9]** | **2 (66.7%) [8]** | **7 (70.0%) [17]** |
| Cerebrovascular Accident | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Dizziness | 2 (28.6%) [2] | 0 (0.0%) [0] | 2 (20.0%) [2] |
| Generalised Tonic-Clonic Seizure | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Haemorrhage Intracranial | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Headache | 1 (14.3%) [1] | 2 (66.7%) [2] | 3 (30.0%) [3] |
| Hemianopia | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Lethargy | 2 (28.6%) [2] | 0 (0.0%) [0] | 2 (20.0%) [2] |
| Neuralgia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Neuropathy Peripheral | 1 (14.3%) [1] | 1 (33.3%) [1] | 2 (20.0%) [2] |
| Paraesthesia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Presyncope | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Transverse Sinus Thrombosis | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| **Psychiatric disorders** | **1 (14.3%) [1]** | **1 (33.3%) [2]** | **2 (20.0%) [3]** |
| Insomnia | 1 (14.3%) [1] | 1 (33.3%) [2] | 2 (20.0%) [3] |
| **Renal and urinary disorders** | **3 (42.9%) [3]** | **2 (66.7%) [3]** | **5 (50.0%) [6]** |
| Dysuria | 2 (28.6%) [2] | 1 (33.3%) [2] | 3 (30.0%) [4] |
| Haematuria | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Pollakiuria | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Reproductive system and breast disorders** | **5 (71.4%) [7]** | **2 (66.7%) [2]** | **7 (70.0%) [9]** |
| Pelvic Discomfort | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Pelvic Floor Muscle Weakness | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Pelvic Pain | 3 (42.9%) [3] | 0 (0.0%) [0] | 3 (30.0%) [3] |
| Premature Menopause | 2 (28.6%) [2] | 0 (0.0%) [0] | 2 (20.0%) [2] |
| Vaginal Haemorrhage | 1 (14.3%) [1] | 1 (33.3%) [1] | 2 (20.0%) [2] |
| **Respiratory, thoracic and mediastinal disorders** | **3 (42.9%) [4]** | **0 (0.0%) [0]** | **3 (30.0%) [4]** |
| Cough | 2 (28.6%) [3] | 0 (0.0%) [0] | 2 (20.0%) [3] |
| Dyspnoea | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Skin and subcutaneous tissue disorders** | **3 (42.9%) [5]** | **1 (33.3%) [1]** | **4 (40.0%) [6]** |
| Alopecia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Rash Maculo-Papular | 1 (14.3%) [3] | 0 (0.0%) [0] | 1 (10.0%) [3] |
| Skin Exfoliation | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Skin Reaction | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Vascular disorders** | **3 (42.9%) [3]** | **1 (33.3%) [1]** | **4 (40.0%) [4]** |
| Flushing | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Hot Flush | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Hypertension | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Hypotension | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |

[1] Percentages are based on the number of patients on the dose level

**Reported Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) – Evaluable population**

| | Dose Level | | |
|---|---|---|---|
| | **90mg (n=7)** | **120mg (n=3)** | **Total (n=10)** |
| **Number of patients experiencing at least one SAE/SAR/SUSAR - n (%)[1]** | 3 (42.9%) | 1 (33.3%) | 4 (40.0%) |
| **Number of SAE/SAR/SUSAR per patient (for patients with at least one SAE/SAR/SUSAR) – median (range)** | 1 (1 to 1) | 4 (4 to 4) | 1 (1 to 4) |
| **Overall Assessment - n (%)[2,3]** | | | |
| SUSAR (Suspected Unexpected Serious Adverse Reaction) | 1 (33.3%) | 4 (100%) | 5 (71.4%) |
| SAR (Serious Adverse Reaction) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| SAE (Serious Adverse Event) | 2 (66.7%) | 0 (0.0%) | 2 (28.6%) |
| Not SAE | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pending | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Total** | **3 (100%)** | **4 (100%)** | **7 (100%)** |
| **CTCAE v5.0 grade - n (%)[2]** | | | |
| 1 – Mild | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 2 – Moderate | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| 3 – Severe | 2 (66.7%) | 2 (50%) | 4 (57.1%) |
| 4 – Life threatening | 0 (0.0%) | 2 (50%) | 2 (28.6%) |
| 5 – Death related to AE | 1 (33.3%) | 0 (0.0%) | 1 (14.3%) |
| Pending | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Total** | **3 (100%)** | **4 (100%)** | **7 (100%)** |
| **Why was the event serious - n (%)[2]** | | | |
| 1 – Resulted in death | 1 (33.3%) | 0 (0.0%) | 1 (14.3%) |
| 2 – Life threatening | 0 (0.0%) | 2 (50%) | 2 (28.6%) |
| 3 – Required hospitalisation or prolongation of existing hospitalisation | 2 (66.7%) | 0 (0.0%) | 2 (28.6%) |
| 6 - Other important medical event | 0 (0.0%) | 2 (50%) | 2 (28.6%) |
| **Total** | **3 (100%)** | **4 (100%)** | **7 (100%)** |

[1] Percentages are based on the number of patients on the dose level
[2] Percentages are based on the number of SAEs/SARs/SUSARs.
[3] Taken as the 'worst case' of the PI and independent clinical reviewer assessments

**Summary by SOC and PT term as reported on the SAE form – Evaluable population**

| | Dose Level | | |
|---|---|---|---|
| | **90mg (n=7)** | **120mg (n=3)** | **Total (n=10)** |
| **Number of patients that experienced at least one SAE - n (%) [no. of events]** | **3 (42.9%) [3]** | **1 (33.3%) [4]** | **4 (40.0%) [7]** |
| **Summary of SAEs - n (%)[1] [no. of events]** | | | |
| **Gastrointestinal disorders** | **1 (14.3%) [1]** | **0 (0.0%) [0]** | **1 (10.0%) [1]** |
| Small Intestinal Obstruction | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Infections and infestations** | **1 (14.3%) [1]** | **0 (0.0%) [0]** | **1 (10.0%) [1]** |
| Pneumonia | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| **Nervous system disorders** | **1 (14.3%) [1]** | **1 (33.3%) [4]** | **2 (20.0%) [5]** |
| Cerebrovascular Accident | 1 (14.3%) [1] | 0 (0.0%) [0] | 1 (10.0%) [1] |
| Generalised Tonic-Clonic Seizure | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Haemorrhage Intracranial | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Hemianopia | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |
| Transverse Sinus Thrombosis | 0 (0.0%) [0] | 1 (33.3%) [1] | 1 (10.0%) [1] |