**Summary of adverse events**

All subjects had at least one treatment emergent adverse event (TEAE) and the majority of subjects (58 [95.1%]) had at least one treatment-related TEAE. Many of the TEAEs reported were typical of those seen in cancer patients with advanced disease.

The incidence of TEAEs was dose-related. There was no apparent difference between the 3-weekly and weekly schedules in the small number of subjects treated.

Most subjects experienced TEAEs during the first week of treatment. A greater number of TEAEs were reported within 24 hours of dosing after the first dose in Cycle 1 than after the second and third doses in Cycle 1. Additionally, the frequency of adverse events was higher after the first dose in Cycle 1 than after the first dose in later cycles.

The most common TEAEs related to general disorders (60 [98.4%] subjects), gastrointestinal disorders (46 [75.4%]), musculoskeletal and connective tissue disorders (40 [65.6%)] subjects, metabolism and nutrition disorders (38 [62.3%] subjects) and investigations (38 [62.3%] subjects). Furthermore adverse events relating to general disorders, gastrointestinal disorders and investigations considered treatment-related were reported in the majority of subjects occurring in 56 (91.8%), 36 (59.0%) and 34 (55.7%), respectively.

The most common preferred terms were pyrexia and chills, reported by 45 (73.8%) and 41 (67.2%) subjects, respectively. With the exception of two subjects receiving $6 \times 10^{12}$ viral particles (vp) with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 pyrexia, all events were Grade 1 or 2. These usually had onset within 24 hours of dosing.

CTCAE ≥Grade 3 TEAEs were reported in a higher proportion of subjects receiving doses of $3 \times 10^{12}$ vp and above and the number of these severe 3 TEAEs reported per subject also increased with dose. The most frequent CTCAE Grade 3 and above TEAEs were as a result of laboratory test findings. Hypertension was the most reported Grade 3 preferred term on 25 occasions in 13 (21.3%) subjects but with no apparent dose relationship.

Three (4.9%) subjects had adverse events with outcome death, none were considered treatment-related.

A total of 37 SAEs were reported in 20 (32.8%) subjects. The incidence of SAEs appeared to be dose-related. Treatment-related SAEs were only reported at doses of $3 \times 10^{12}$ vp and above The majority were single cases. There were seven reports of obstruction of the intestines which were considered treatment-related in two subjects who had other predisposing conditions, such as a history of abdominal surgery and peritoneal metastases, although the obstruction could also be explained by tumour flare. Other SAEs occurring in more than one subject were hypoxia, pyrexia and dyspnoea in three, three and two subjects, respectively.

Dose limiting toxicities of acute lung injury and dyspnoea with hypoxia were experienced after the first dose with $1 \times 10^{13}$ vp in the Phase I Dose Escalation Stage. This dose was therefore determined as not tolerated. The maximum tolerated dose at the end of Phase I was determined to be $6 \times 10^{12}$ vp over 40 minutes. In Phase Ib, the overall frequency and severity of TEAEs including severe hypoxia and increased transaminases following doses of $6 \times 10^{12}$ vp resulted in this dose being determined as not tolerated and the maximum tolerated dose was re-evaluated as $3 \times 10^{12}$ vp.

Adverse events resulted in permanent study treatment discontinuation in seven (11.4%) subjects; these events occurred early and led to discontinuation during the first cycle in four subjects. An overall summary of TEAEs is given in Table 1 and common related TEAEs occurring in 10% and more of subjects is given in Table 2. TEAEs reported in 5% or more of subjects are in a separate attachment.

**Table 1 Overall Summary of Treatment Emergent Adverse Events (Safety Population)**

| **Number of Subjects with:** | **<1 x $10^{12}$ vp N=6** | **1-3 x $10^{12}$ vp N=26** | **>3 x $10^{12}$ vp N=29** | **Total N=61** |
|---|---|---|---|---|
| Any TEAE | 6 (100.0%) | 26 (100.0%) | 29 (100.0%) | 61 (100.0%) |
| Any treatment-related TEAE[a] | 4 (66.7%) | 25 (96.2%) | 29 (100.0%) | 58 (95.1%) |
| SAE | 1 (16.7% | 7 (26.9%) | 12 (41.4%) | 20 (32.8%) |
| Treatment-related SAE[a] | 0 | 4 (15.4%) | 6 (20.7%) | 10 (16.4%) |
| DLT | 0 | 2 (7.7%) | 6 (20.7%) | 8 (13.1%) |
| TEAE leading to study treatment discontinuation | 0 | 4 (15.4%) | 3 (10.3%) | 7 (11.5%) |
| Treatment related TEAE leading to study treatment discontinuation | 0 | 3 (11.5%) | 3(10.3%) | 6 (9.8%) |
| TEAE with outcome death | 1 (16.7%) | 1 (3.8%) | 1(3.4%) | 3 (4.9%) |
| Treatment related TEAE with outcome death | 0 | 0 | 0 | 0 |

Abbreviations: DLT=dose limiting toxicity; SAE=serious adverse event; TEAE=treatment emergent adverse event

[a] Possibly, probably or definitely related to study treatment

**Table 2 Related Treatment-Emergent Adverse Events Occurring in 10% or more of Subjects (Safety Population)**

| MedDRA Version 19.1 Preferred Term | Dose Level Assigned (vp) | | | |
|---|---|---|---|---|
| | **<1 x $10^{12}$ vp N=6** | **1 to 3 x $10^{12}$ vp N=26** | **>3 x $10^{12}$ vp N=29** | **All Doses N=61** |
| Pyrexia | 1 (16.7%) | 19 (73.1%) | 23 (79.3%) | 43 (70.5%) |
| Chills | | 18 (69.2%) | 23 (79.3%) | 41 (67.2%) |
| Fatigue | 2 (33.3%) | 8 (30.8%) | 11 (37.9%) | 21 (34.4%) |
| Nausea | | 11 (42.3%) | 10 (34.5%) | 21 (34.4%) |
| Vomiting | | 8 (30.8%) | 9 (31.0%) | 17 (27.9%) |
| Asthenia | 1 (16.7%) | 8 (30.8%) | 7 (24.1%) | 16 (26.2%) |
| Decreased appetite | | 11 (42.3%) | 5 (17.2%) | 16 (26.2%) |
| Diarrhoea | | 4 (15.4%) | 10 (34.5%) | 14 (23.0%) |
| Influenza like illness | | 7 (26.9%) | 6 (20.7%) | 13 (21.3%) |
| Alanine aminotransferase increased | | 1 ( 3.8%) | 11 (37.9%) | 12 (19.7%) |
| Fibrin D dimer increased | | 4 (15.4%) | 8 (27.6%) | 12 (19.7%) |
| Hypertension | 1 (16.7%) | 6 (23.1%) | 5 (17.2%) | 12 (19.7%) |
| Musculoskeletal pain | 1 (16.7%) | 4 (15.4%) | 6 (20.7%) | 11 (18.0%) |
| Thrombocytopenia | | 2 ( 7.7%) | 9 (31.0%) | 11 (18.0%) |
| Aspartate aminotransferase increased | | 1 ( 3.8%) | 9 (31.0%) | 10 (16.4%) |
| Platelet count decreased | 1 (16.7%) | 3 (11.5%) | 5 (17.2%) | 9 (14.8%) |
| Proteinuria | | 4 (15.4%) | 5 (17.2%) | 9 (14.8%) |
| Headache | | 3 (11.5%) | 4 (13.8%) | 7 (11.5%) |
| Hypocalcaemia | | 3 (11.5%) | 4 (13.8%) | 7 (11.5%) |
| Hypophosphataemia | | 3 (11.5%) | 4 (13.8%) | 7 (11.5%) |

Abbreviations: MedDRA=Medical dictionary for drug regulatory activities; vp=viral particles

Number and percentage of subjects with each preferred term are shown. Commonly reported treatment-related TEAEs were defined as those possibly, probably or definitely related to study treatment or the relationship is unknown occurring in ≥10% subjects overall in Phase I and Phase Ib combined

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