**Supplementary Data**

**Supplementary Table 1:** Summary of pharmacokinetic parameters (days 1 and 15).

| **Metric** | **Dose-Escalation Phase** |  | **Expansion Cohort Phase** |
| --- | --- | --- | --- |
| **Day 1** |  | **Day 15** | **Day 1** | **Day 15** |
| **Cohort 1 (30 mg) (n=6)** | **Cohort 2 (45 mg) (n=6)** | **Cohort 1 (30 mg) (n=6)** | **Cohort 2 (45 mg) (n=6)** | **Cohort 1 (30 mg) (n=31)** | **Cohort 1 (30 mg) (n=31)** |
| AUC0-24 (ng•h/mL) |
| Mean | 291 | 375 |  | 1103 | 1197 |  | 217  | 747  |
| %CV | 24·5 | 43·7 |  | 48·8 | 47·2 |  | 37·0 | 71·8 |
| Minimum, Maximum | 197, 394 | 225, 595 |  | 612, 2080 | 452, 1864 |  | 76·3, 385 | 207, 2938 |
| C24(ng/mL) |
| Mean | 8·91 | 9·88 |  | 40·5 | 38·5 |  | 6·23  | 26·0  |
| %CV | 32·4 | 44·9 |  | 64·8 | 43·6 |  | 50·5 | 102 |
| Minimum, Maximum | 5·22, 13·0 | 5·67, 16·3 |  | 18·6, 89·8 | 14·1, 56·3 |  | 1·81, 17·44 | 7·91, 155 |
| Cmax (ng/mL) |
| Mean | 19·4 | 27·9 |  | 69·2 | 72·3 |  | 18·8  | 48·3  |
| %CV | 33·6 | 33·6 |  | 40·3 | 41·3 |  | 45·6 | 67·5 |
| Minimum, Maximum | 12·2, 28·0 | 17·3, 41·2 |  | 35·6, 115 | 39·8, 109 |  | 6·34, 34·4 | 13·8, 167 |
| Tmax (h) |
| Median | 3·5 | 3·5 |  | 3·0 | 3·0 |  | 3·0 | 3·0 |
| Minimum, Maximum | 3, 4 | 3, 6 |  | 1, 8 | 1, 8 |  | 1, 8 | 1, 24 |
| CL/F (L/h) Mean |  |  |  | 32.0 | 48.1 |  | 61.0 | 56.0 |
| %CV |  |  |  | 39.5 | 59.8 |  | 36.2 | 57.7 |
| Minimum |  |  |  | 14.4 | 24.1 |  | 28.5 | 10.2 |
| Maximum |  |  |  | 49.0 | 99.5 |  | 119 | 145 |
| AUC0-24=area under the concentration-time curve from time 0 (predose) to 24 hours. C24=plasma concentration 24 hours after dose administration. CL/F=oral clearance. Cmax=maximum plasma concentration. CV=coefficient of variation. Tmax=time of maximum concentration. |

**Supplementary Table 2:** Significant changes in circulating biomarkers from baseline.

|  |  |  |  |
| --- | --- | --- | --- |
| **CAF**  | **Day** | **Percentage Change** | **p Value** |
| ANG2 | 15 | −24 | 0·0001 |
| ANG2 | 22 | −17 | 0·0055 |
| Clusterin | 8 | 25 | 0·0017 |
| Clusterin | 22 | 23 | 0·0003 |
| FASL | 8 | 26 | 0·0001 |
| FASL | 15 | 20 | 0·0001 |
| FASL | 22 | 44 | 0·0001 |
| GCSF | 8 | 46 | 0·0018 |
| IGFBP3 | 8 | 19 | 0·0022 |
| IGFBP3 | 15 | 13 | 0·0086 |
| IGFBP3 | 22 | 17 | 0·0084 |
| IL6 | 8 | 58 | 0·0001 |
| IL6 | 15 | 124 | 0·0001 |
| IL6 | 22 | 111 | 0·0001 |
| IL8 | 15 | 20 | 0·0086 |
| PlGF | 8 | 105 | 0·0001 |
| PlGF | 15 | 130 | 0·0001 |
| PlGF | 22 | 120 | 0·0001 |
| SCF | 15 | −14 | 0·0055 |
| TRAIL | 8 | 25 | 0·0001 |
| TRAIL | 15 | 17 | 0·0027 |
| TRAIL | 22 | 24 | 0·0013 |
| TSP2 | 8 | −14 | 0·004 |
| TSP2 | 15 | −19 | 0·0011 |
| VCAM1 | 8 | 28 | 0·0001 |
| VCAM1 | 15 | 43 | 0·0001 |
| VCAM1 | 22 | 64 | 0·0001 |
| VEGF | 8 | 61 | 0·0001 |
| VEGF | 15 | 83 | 0·0001 |
| VEGF | 22 | 83 | 0·0001 |
| VEGFR2 | 15 | −21 | 0·0001 |
| VEGFR2 | 22 | −21 | 0·0001 |
| sMET | 8 | 12 | 0·0001 |

ANG2=angiopoietin 2. CAF=cytokines and angiogenic factor. FASL=Fas ligand. G-CSF=granulocyte colony–stimulating factor. IGFBP1=insulin-like growth factor–binding protein 1. IL=interleukin. PlGF=placental growth factor. sMET=soluble MET. TRAIL=tumour necrosis factor–related apoptosis-inducing ligand. TSP2=thrombospondin 2. VCAM=vascular cell adhesion molecule 1. VEGFR=vascular endothelial growth factor. VEGFR=vascular endothelial growth factor receptor.

**Supplementary Table 3:** Multivariate models for selected covariates, Overall Survival.

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Pvalue | Hazard Ratio | 95% Confidence Limits |
| IL6 | 0.0292 | 1.637 | 1.051 | 2.55 |
| Age | 0.8296 | 0.994 | 0.942 | 1.049 |
| Sex (M vs F) | 0.783 | 0.821 | 0.202 | 3.337 |
| ECOG (Symptomatic vs Normal) | 0.7157 | 1.461 | 0.19 | 11.259 |
| HEPINF (Current vs None, Past) | 0.124 | 0.35 | 0.092 | 1.333 |
| Cirrhosis (Current vs None) | 0.7475 | 0.781 | 0.174 | 3.514 |
| BMI | 0.8835 | 1.015 | 0.836 | 1.231 |
| SLD | 0.3577 | 1.007 | 0.992 | 1.022 |

HEPINF – current or past hepatitis infection, SLD – baseline sum of longest diameters

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Pvalue | Hazard Ratio | 95% Confidence Limits |
| IL8 | 0.0005 | 3.826 | 1.79 | 8.178 |
| Age | 0.383 | 1.03 | 0.964 | 1.102 |
| Sex (M vs F) | 0.2582 | 0.414 | 0.09 | 1.908 |
| ECOG (Symptomatic vs Normal) | 0.0599 | 7.035 | 0.922 | 53.683 |
| HEPINF (Current vs None, Past) | 0.1052 | 0.316 | 0.078 | 1.273 |
| Cirrhosis (Current vs None) | 0.0327 | 0.116 | 0.016 | 0.837 |
| BMI | 0.3134 | 0.9 | 0.734 | 1.104 |
| SLD | 0.9717 | 1 | 0.985 | 1.015 |

HEPINF – current or past hepatitis infection, SLD – baseline sum of longest diameters

**Supplementary Figure Legends**

**Supplementary Figure 1.** Association of NR1I3 haplotype with TTP (Supplementary On-line only). CAT/CAT carriers, median TTP 1.92 months vs 6.21 months for CAT/− or −/− carriers.