A randomized Phase I trial evaluating safety and pharmacokinetics of single and multiple ascending doses of eclitasertib, a RIPK1 inhibitor, in healthy participants

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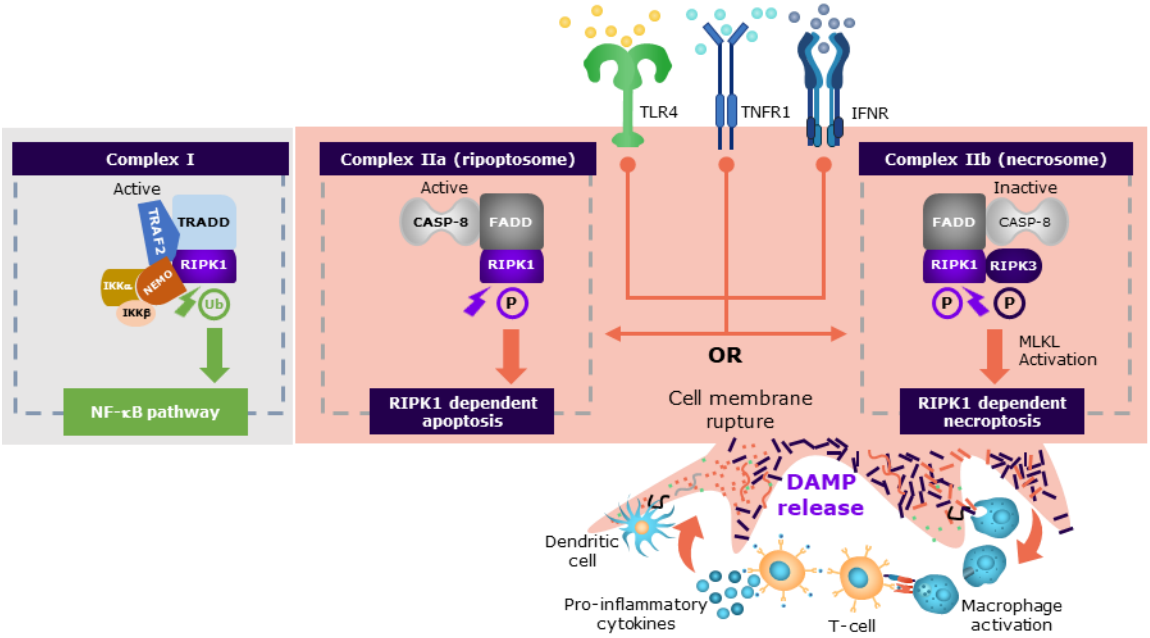
Running title: Safety, PK and PD of RIPK1 inhibitor eclitasertib in healthy participants

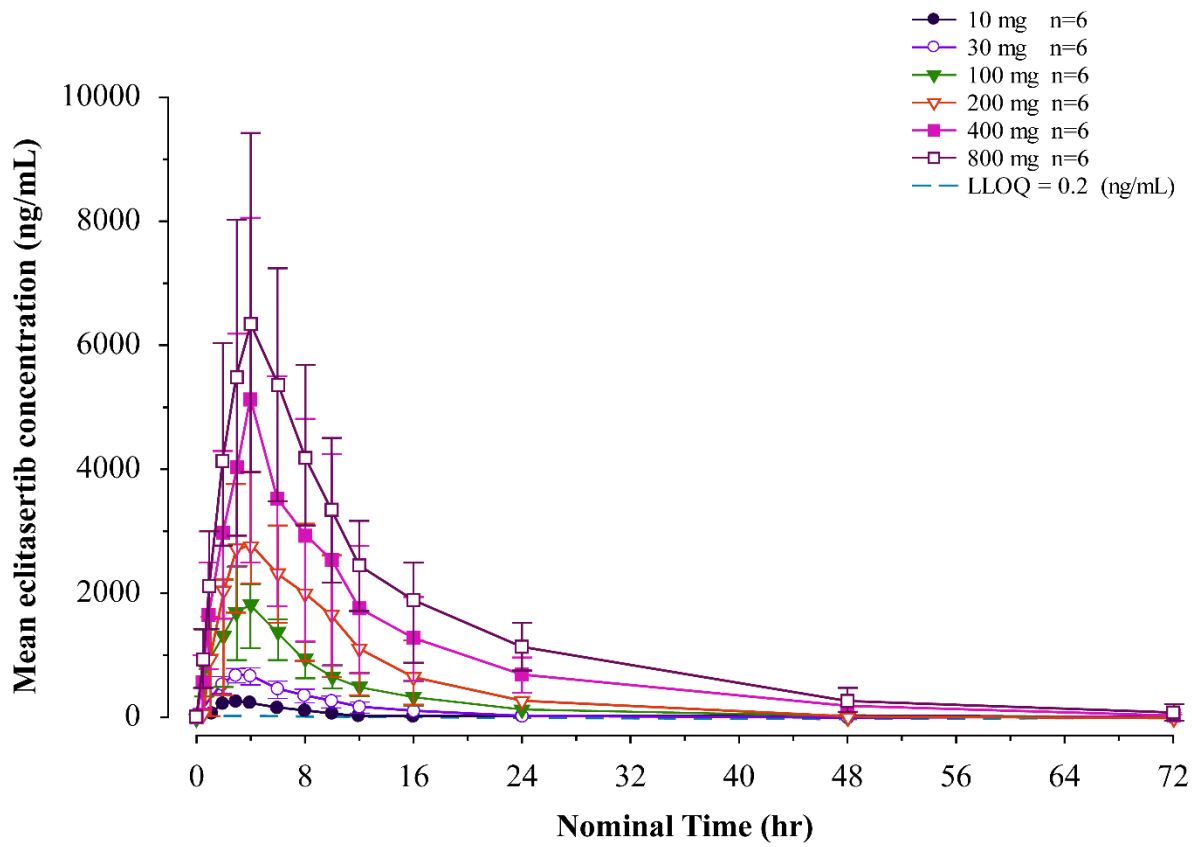
Supplementary figure S1 Regulation of programmed cell-death pathways by RIPK1

Kinase activity of RIPK1 drives caspase-8 dependent apoptosis or necroptosis in presence of RIPK3 and MLKL.



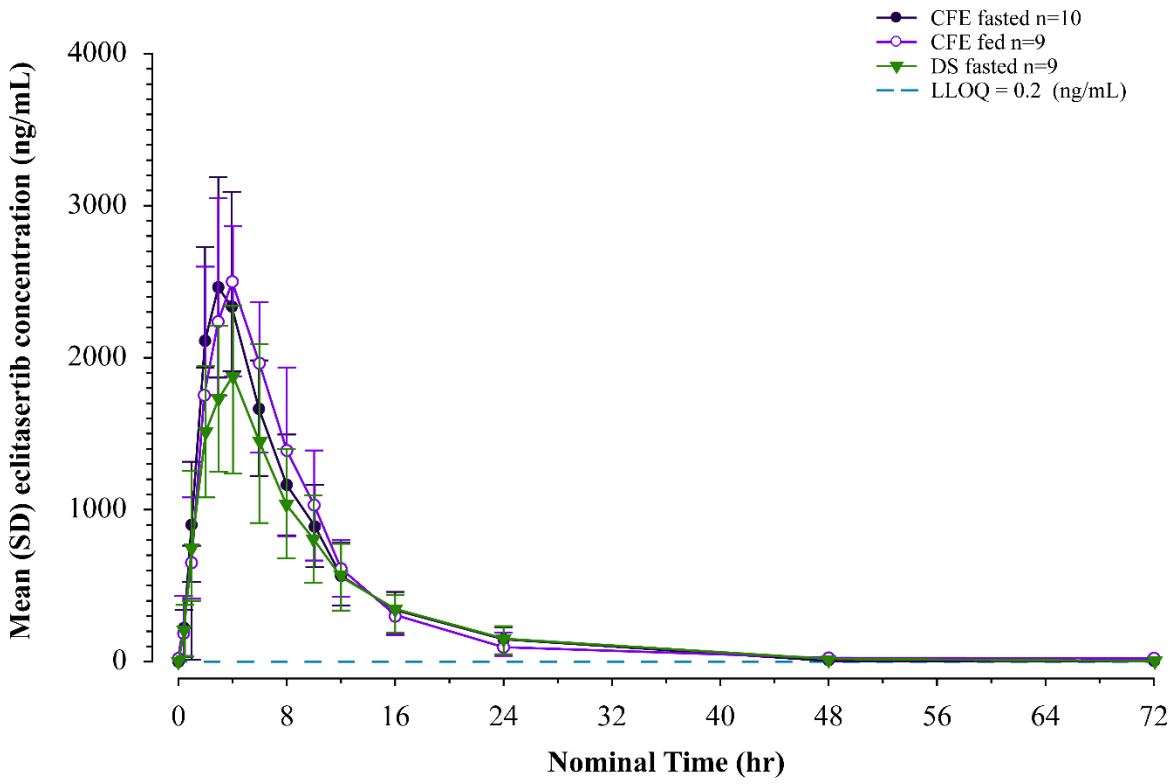
CASP-8, caspase-8; DAMP, damage-associated molecular pattern; FADD, Fas-associated death domain protein; IFNR, interferon receptor; IKK, IkB kinase; MLKL, mixed lineage kinase domain like pseudokinase; NEMO, NF-kB essential modulator; NF-kB, nuclear factor kappa B; RIPK1, receptor interacting protein kinase; TLR4, toll-like receptor 4; TNFR1, tumor necrosis factor receptor 1; TRADD; TNF receptor-associated death domain protein; TRAF2; TNF receptor associated factor 2

Supplementary Figure S2: Mean plasma concentration versus time following single oral administration of 10–800 mg eclitasertib



LLOQ, lower limit of quantification

Supplementary Figure S3: **Mean plasma concentration versus time profiles after single administration of 100 mg eclitasertib as CFE formulation in fasted or fed conditions and as DS formulation in fasted conditions**



CFE, prototype capsule formulation of eclitasertib; DS, drug substance in capsule form; LLOQ, lower limit of quantification

Supplementary Figure 4: Mean plasma concentration versus time profiles after administration of eclitasertib 50–600 mg on Day 1 (a) and after 14-days of once-daily administration on Day 14 (b)