Ph2a dose selection based on the relationship between PK and Target Occupancy

CNS Session - EMA/EFPIA Workshop on the importance of Dose finding and dose selection

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Background

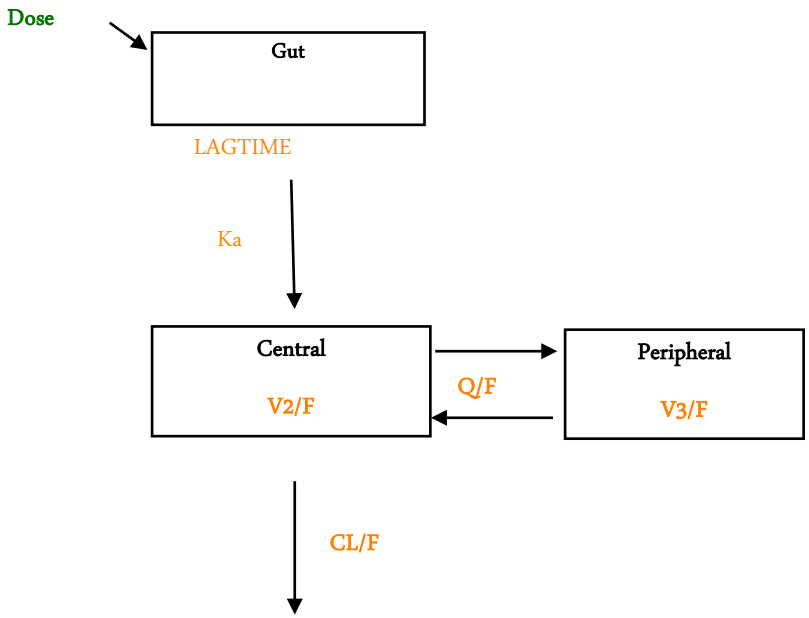
- Small molecule from the CNS portfolio
- Phase 1 studies completed in healthy volunteers:
  - Single ascending dose
  - Multiple ascending dose
  - PET study
- Uncertainty around the target occupancy (TO) needed at steady state for efficacy in the patient population
- Which doses should be tested in Phase 2a to characterize the TO – Efficacy relationship?

Clinical Pharmacology proposals

- To build a Population Pharmacokinetic model using Phase 1 data
- To build a PKPD model for target occupancy using PET data
- To simulate Target Occupancy time profiles at steady-state by dose
- To compute the % of measurements where Target Occupancy was within given ranges over the dosing interval
- To determine the optimal number of doses that should be tested in Phase 2a to characterize the TO – Efficacy relationship

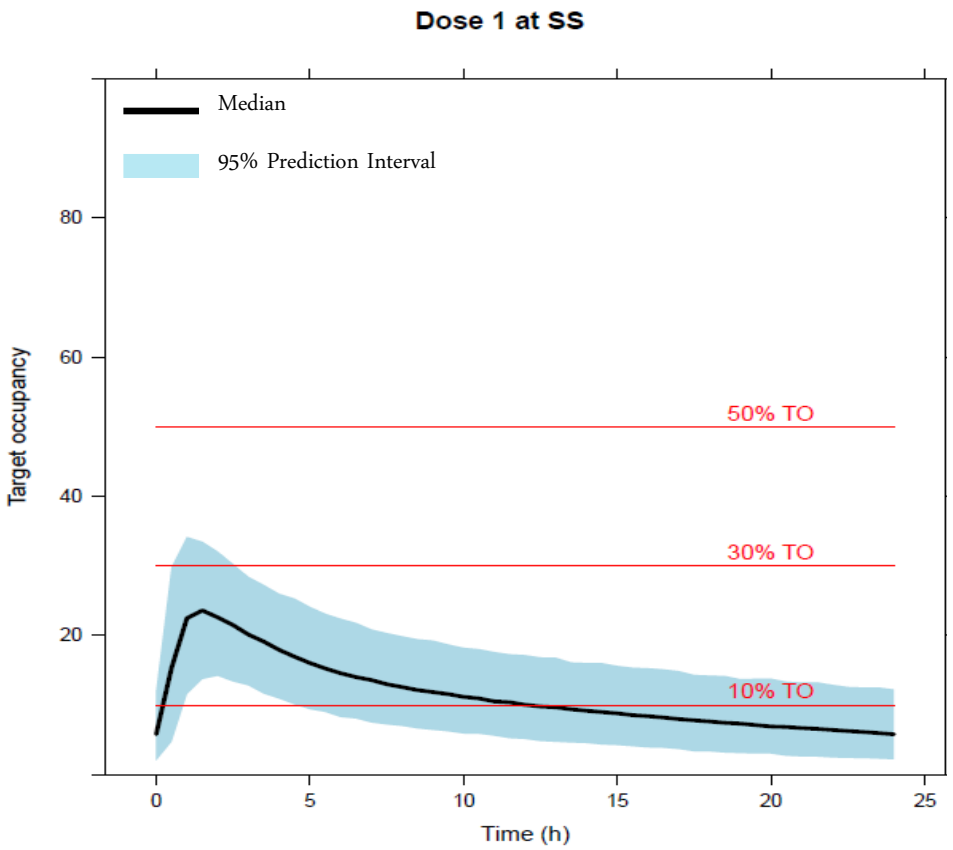
PK and PKPD models

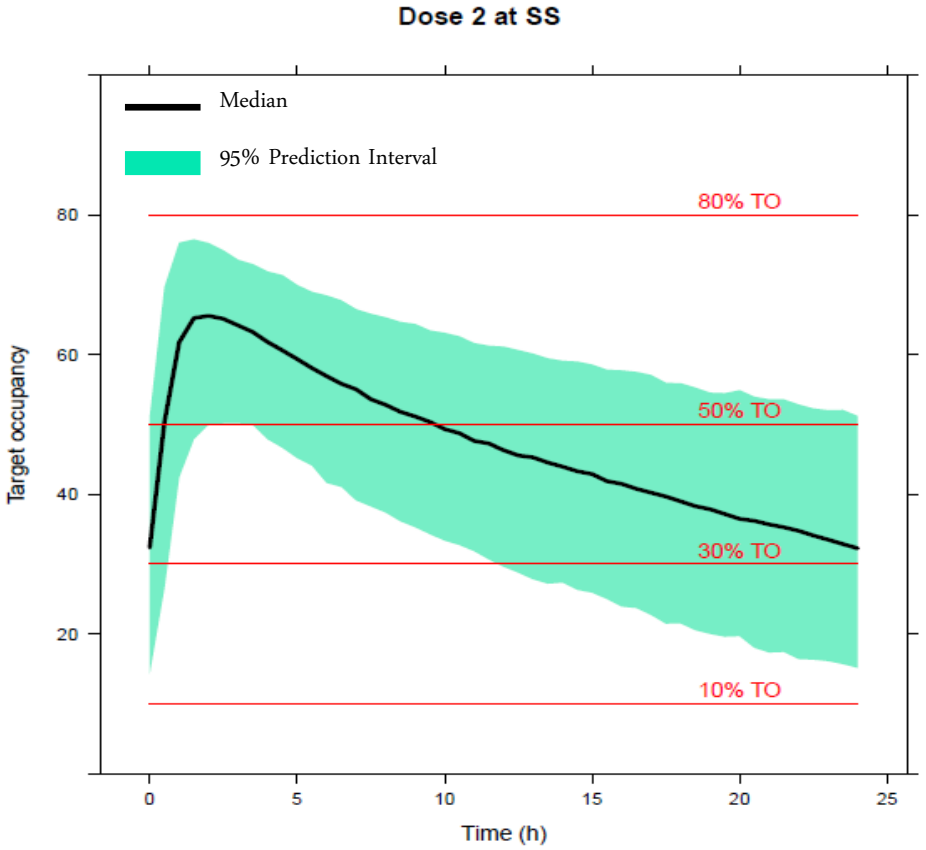
- A two-compartment Population PK model with first order absorption adequately described the PK profile



- An Emax PKPD model adequately described the PK/Target Occupancy relationship

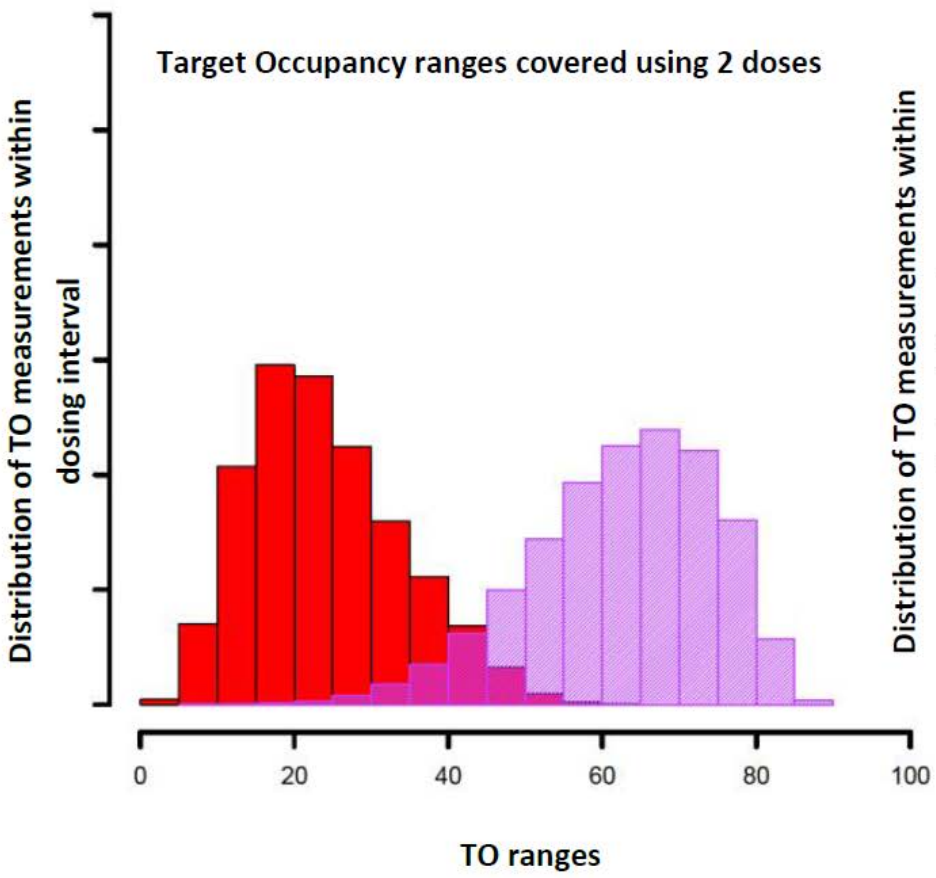
Simulated Target Occupancy time profiles at Steady State

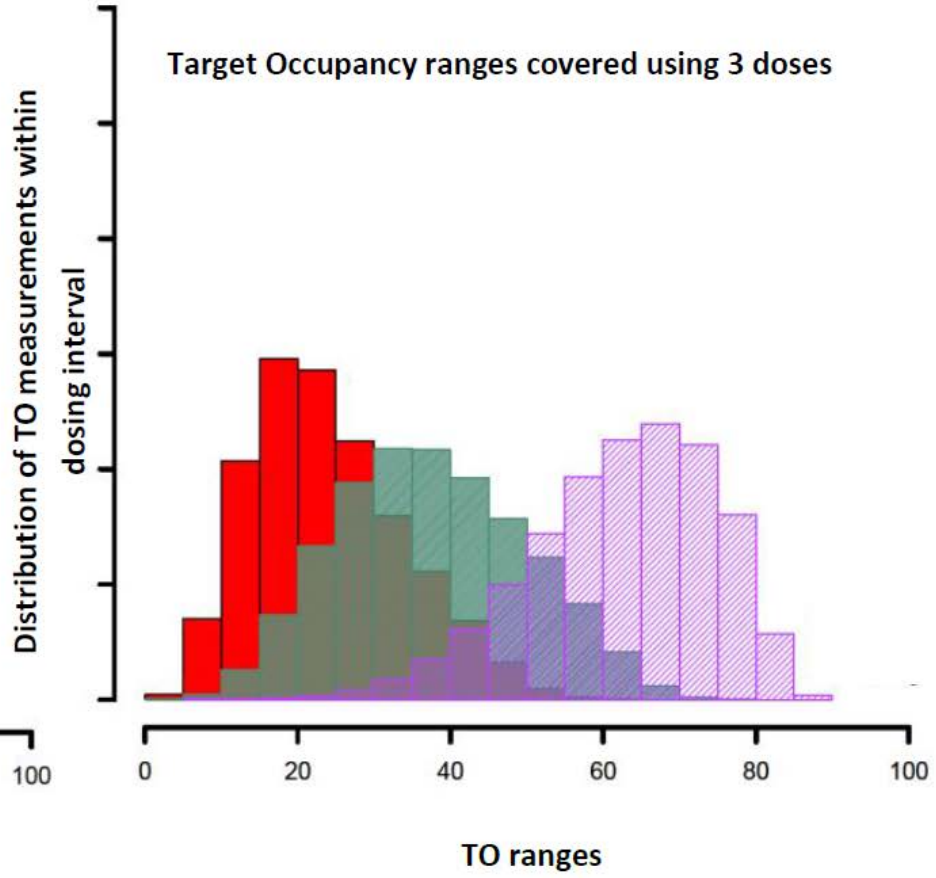




	Percentage of hourly simulated measurements within TO ranges		
TO Ranges	10-30% TO	30-50% TO	50-80% TO
Dose 1	52	1	0
Dose 2	10	48	42

Optimal coverage of Target Occupancy achieved with 3 doses





Conclusions

- Population PK and PKPD models were used to simulate Target Occupancy time profiles at steady state by dose
- Doses that cover optimally the target occupancy ranges over the dosing interval were identified
- Phase 1 data were leveraged using simple modeling methods that translated into powerful graphical representation to support dose selection
- Team was open and valued the recommendation


Q&A

Doing now what patients need next