Predictive Performance of Bayesian and Population Pharmacokinetic (POP PK) Analysis Approaches for Prediction of Exposure During First Time in Human (FTiH) Dose Escalation

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Introduction

- Placebo-controlled, randomized, dose-escalation, First Time in Human (FTiH) study.
- 2 part study:
  - Part A: Single dose (N=9; 6 active, 3 placebo), first dose of 5mg.
  - Part B: Repeat dose – 1 dose a day for 14 days (N=10; 8 active, 2 placebo)
- Exposures in the FTiH study were limited to predefined levels such that a proposed dose was acceptable if the predicted probability of any individual exceeding the Area Under the Curve from 0 to 24 hours (AUC(0-24)) (4900 ng.h/mL) or Maximum Concentration (Cmax) (443 ng/mL) limits was no more than 10%.

Methods

Population Pharmacokinetic (POP PK) Approach

- Fit-for-purpose population pharmacokinetic (PK) mixed effect models were developed (NONMEM v7.2) after each single dose escalation step and after 5 mg repeat dose.
- Concentration-time data were adequately described by a 2 compartment model with first-order absorption. Parameters were generally well defined with standard errors typically less than 30% with increasing precision as the data size increased. Inter-individual variability was estimated on up to four parameters [oral clearance (CL/F), central and peripheral volume of distribution (Vc/F and Vp/F), and absorption rate constant (KA)] and was typically <30% except on KA (77 to 101%). Visual and numerical predictive checks demonstrated adequate model performance.
- Clinical trial simulations were conducted by incorporating parameter uncertainty (mrgsolve in R) and provided the probabilities for individual subjects to exceed exposure limits for higher single and repeat doses.

Bayesian Approach

- Bayesian analysis after data from 3 dose levels available, to obtain predictive probabilities of exceeding exposure limits.
- Power model: $y = \exp(\theta_1 + \varepsilon) \cdot \text{dose}^{\theta_2}$ (1)
- θ_s, s=1,2, were estimated by linear regression of the $\log_e$-transformed PK parameters on $\log_e$ dose levels.

$$\log(y_{ij}) = \theta_1 + \theta_2 \cdot \log(d_{ij}) + \varepsilon_{ij}$$

Where:

- y_{ij} is the observed or predicted PK variable of the j-th dose d_{ij} administered to the i-th subject. i.e. AUC[0-24] or Cmax.
- θ_1, θ_2 are population intercept and slope, respectively.
- ϵ_{ij} is a random error term, with mean zero and precision σ^2.
- Non-informative priors for θ_1, θ_2 and σ^2, due to limited information.
- Analysis performed using SAS V9.4.

Results

In the following tables, figures in red show lowest dose at which the 10% threshold is crossed for each modelling approach.

Predictive probabilities for Single Dosing

Dose Escalation Analysis 1

Dose (mg)	AUC(0-24) Probability (%)	Cmax Probability (%)
5	0	0
15	0	0
25	0	0
30	0	7
35	0	23
40	4	27

Data: 5 mg single dose (n=5).
POP PK Approach: 100 trials, n=6/trial
Decision: 15mg single dose

Dose Escalation Analysis 2

Dose (mg)	AUC(0-24) Probability (%)	Cmax Probability (%)
5	0	0
15	0	0
25	0	5.3
30	3.3	20.3
35	20.8	48.3
40	56.8	78.7

Data: 5 mg and 15mg single dose (n=12)
POP PK Approach: 1000 trials, n=6/trial
Decision: 25mg single dose

Dose Escalation Analysis 3

Dose (mg)	POP PK Approach AUC(0-24) Probability (%)	POP PK Approach Cmax Probability (%)	Bayesian Approach AUC(0-24) Probability (%)	Bayesian Approach Cmax Probability (%)
5	0	0		
15	0	0		
25	0.1	5.8		
30	1.5	18	2	8
35	11.9	43.1	7	17
40	39.6	68.3	18	28

Data: 5 mg, 15mg and 25mg single dose data (n=18)
POP PK Approach: 1000 trials, n=6/trial
Bayesian Approach: 10000 individual subject values.
Decision: End single dose

Predictive probabilities for Repeat Dosing

Dose Escalation Analysis 3 for Repeat dosing

Dose (mg)	POP PK Approach AUC(0-24) Probability (%)	POP PK Approach Cmax Probability (%)	Bayesian Approach AUC(0-inf) Probability (%)
5	0	0	0
10	0	0	0.2
15	10	1.4	7
20	79.7	38.8	38
25	100	94.5	75

Data: 5 mg, 15mg and 25mg single dose (n=18)
POP PK Approach: 1000 trials, n=8/trial
Bayesian Approach: 10000 individual subject values.
Decision: 5mg once daily followed by 15mg once daily if exposure for 5mg repeat dose predicted accurately and no safety signals observed.

Retrospective Analysis of Predictive Probabilities for Repeat Dosing

Data: 5 mg, 15mg and 25mg single dose and 5mg repeat dose (n=25)
POP PK Approach: 1000 trials, n=8/trial

Retrospective Analysis (POP PK Approach)

Dose (mg)	AUC(0-24) Probability (%)	Cmax Probability (%)
5	0	0
10	0	0
15	18.5	1
20	100	50.5

Observed Results

The toxicity margin was exceeded only during the 15mg repeat dosing cohort where the AUC(0-24) limit (4900 ng.h/mL) was exceeded by 3/8 subjects (20% maximum). While the model based on single dose data alone slightly under predicted the median steady-state exposure for the 5mg dose and had a predicted probability of an individual subject exceeding the AUC limit ≤ 10%, based on the maximum observed AUC(0-24), it was felt that a 3-fold dose increase should maintain AUC within tox limits. The retrospective analysis with the model based on single dose and 5 mg repeat dose data had a probability of ~20% which was closer to the observed result. In this exercise, the Bayesian approach for predicting repeat dose AUC(0-24) from single dose data relied on PK linearity and time-independence. Although these conditions were approximately met, the single and repeat dosing arms occurred in a small number of different subjects.

Method Comparison

POP PK Approach	Bayesian Approach

• Model includes between subject and residual variability and precision on all parameters
• Assumptions of the underlying distributions:
  • ε ~ N(0,σ^2) – residual variability
  • η ~ N(0,ω^2) – inter-individual variability
  • population parameters log-normally distributed
	• Model includes random error of the *i*-th subject. Planned to include between subject variability however there was not enough data after 3 dose levels to estimate this parameter reliably.
	• The Bayesian predictive distribution fits the model well in terms of the geometric means, but difficult to assess the underlying distribution given small number of subjects.

• Simulate with:
  • Parameter uncertainty and variability
• 1000 trials simulated
  • N=6/trial (single dose)
  • N=8/trial (repeat dose)
• Calculate the # of trials in which at least 1 subject exceeds the exposure limit
	• Simulate distribution of parameter values.
	• Randomly select one parameter value from the distribution and compare with the tox limit.
	• Repeat above steps 10,000 times to obtain a predicted probability.
	• Note, simulations for parameters AUC and Cmax were performed separately.

Conclusions

- Although only a limited number of comparisons could be made, differences in predictive probabilities from the two approaches were observed: while both methods underestimated the probability of any individual exceeding the exposure limits, the POP PK approach provided better predictions overall compared to the Bayesian approach.
- For the POP PK approach, confidence in the predicted probabilities increased with accumulating data, primarily via the bootstrap procedure employed to provide uncertainty estimates in the simulations. The effect of high inter-individual variability and low precision for (certain) parameters when modelling small data sets needs to be considered as this may lead to inflation of variability and over-conservative predictive probability estimates.
- For the Bayesian approach, the use of an informative prior for use in either Part A or Part B, or both, may improve the accuracy of the predictive probabilities. It may be difficult to obtain an informative prior for part A, given the limited information available, but should be possible for Part B when results from the single dosing are available.
- Given the current data, the POP PK approach would be the preferred approach for a future study, of a comparable size, requiring predicted exposure for dose escalation,

References

1. Whitehead J, et al. Biostatistics 2001;2,1.pp.47-61.

Acknowledgements

- Funding for this study (GSK study 201040) was provided by GlaxoSmithKline (clinicaltrials.gov ID: NCT03075410). All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.
- All authors are employees of, and hold shares in, GSK.
- The authors wish to acknowledge Gavin Koh for his critical review during the development of this poster.

Presented at the PSI Conference 2018, Amsterdam, The Netherlands, 03-06 June 2018