

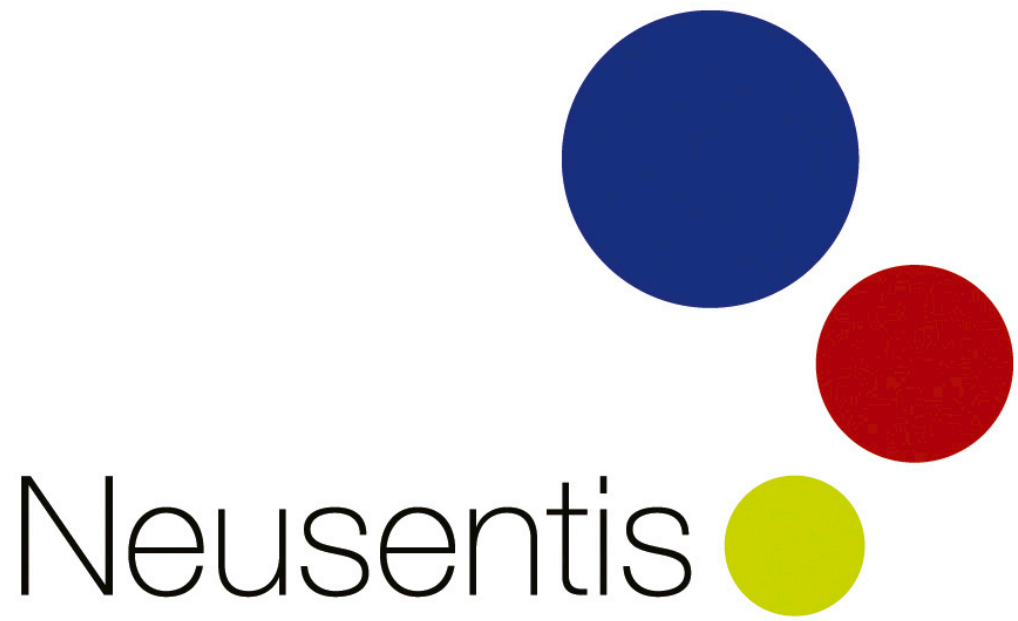


A population PK model combined with PK/PD model for analysis of headache in clinical trials

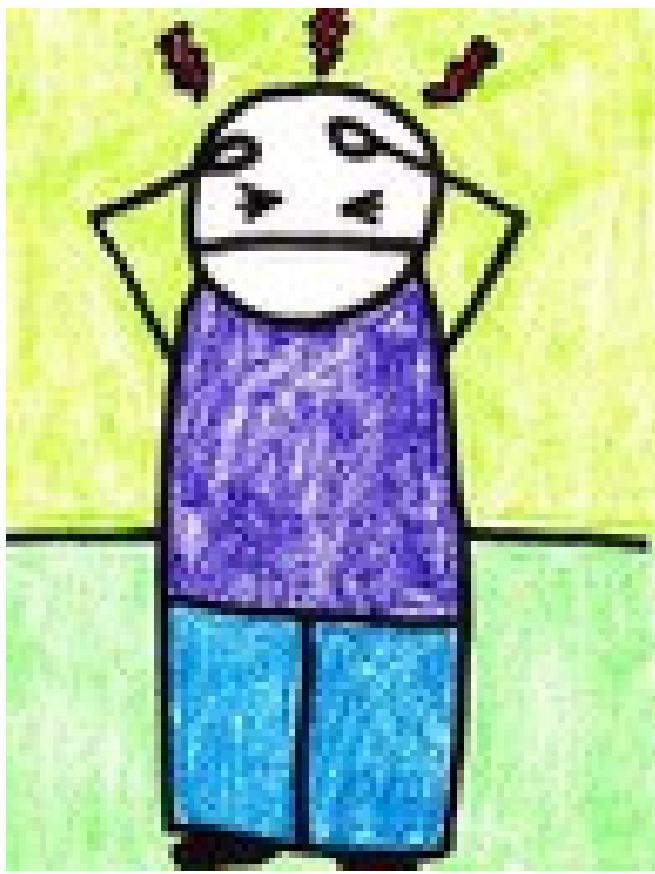
Mark Whitlock, Laura Iavarone

References: 1. Anna Ferrari et al. J Headache Pain (2009) 10:235–239 Focus on headache as an adverse reaction to drugs

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Abstract



Headache was the most common adverse event reported for drug X in phase I clinical trials . Data analysis (from multiple dose studies) suggested that incidence of headaches was related to high exposure of drug X achieved during the first days of treatment. The objective of this analysis was to examine the effect of systemic exposure to drug X on the incidence of headaches with the final aim of proposing a better tolerated dosing regimen for future trials with this drug.

Introduction

Headache is the most common adverse event reported in Phase I clinical studies[1]. Drugs inducing headache as adverse event belong to a variety of therapeutic classes with different mechanisms of action and different toxicity. In the majority of cases the headache has not a typical feature and it is dose dependent. In patients undergoing long-lasting treatments, headache, even if often not considered serious adverse event, might reduce compliance or even cause the interruption of the treatment . A better understanding of factors affecting it to be triggered is therefore essential in order to prevent it or at least to reduce the incidence. The overall incidence of adverse events may sometime be reduced by slower upward dosage titration and despite this is a common strategy used in clinical practice for a variety of different drugs, not much is reported in literature about modelling adverse events with pharmacokinetics with the purpose of quantifying this relationships and use it to guide dose selection for future studies.

Methods

Table 1. Summary clinical studies included in the analysis				
Study	Study Design	Fasted /Fed	Drug X dose	No. of subjects in the dataset
1	Double-blind, randomized, placebo-controlled, parallel-group, escalating multiple-dose study in young, healthy subjects	Fasted	Multiple dose (14 days) as SDD 100 mg BID + 300 mg DL; 200 mg BID; 200 mg BID + 300 mg DL; 300 mg BID + 500 mg DL	32
2	Open-label, parallel-group, multiple dose study in healthy subjects.	Non Fasted	Multiple dose as tablet (14 days): Cohort 1: 200 mg BID + 300 mg DL (3 days); Cohort 2: 200 mg BID + 300 mg DL (5 days)	23
3	Open-label, fixed-sequence, drug interaction study in healthy subjects	Fasted	Multiple dose as SDD: Cohort 1: 100 mg BID Cohort 2: 200 mg BID + 300 mg DL	24

BID = twice daily, DL = dose load

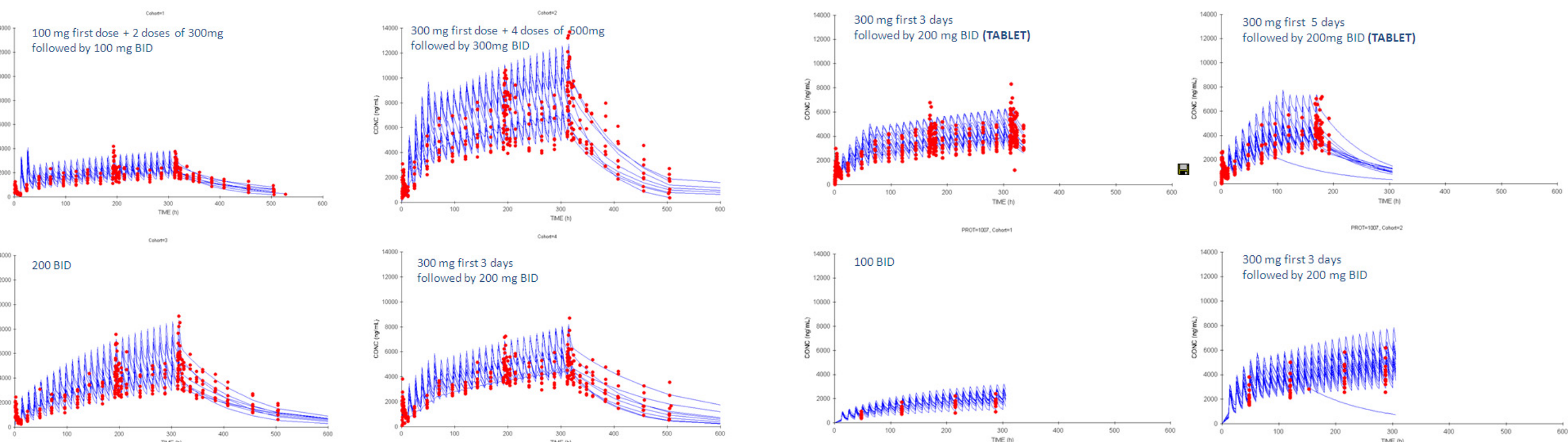
The model was intended to describe PK/PD of drug X in healthy subjects. To that end, the index data file used to develop the models consisted three repeat dose studies (Table 1). Different dose regimens were investigated, all of which involved twice daily (BID) dosing for 14 days. Some of them also involved a loading dose as giving the long half-life of the drug observed in first studies, first attempt was to find a dose regimen which allowed quick achievement of steady state.

The overall analysis consists of two sections: (1) a population PK model to estimate individual exposure, (2) a PK/PD model to correlate individual exposure to severity and duration of headache. For the development of the PK model a dataset of 168 subjects (from either single and repeat dose studies) was used. For the implementation of the PK/PD model of headache the subset of data coming from the repeat dose studies only have been considered. 2 and 3 compartment models with first-order and zero order absorption were evaluated. The effect of covariates such as dose, fed/fasted conditions, formulation (either suspension or tablet) and body weight have been assessed. Individual PK parameter (Cmax, AUCt, cumulative Cmax and cumulative AUCt) values have been estimated for the inclusion in the PK/PD model. The probability of getting a moderate headache was modelled using a mixed effects ordinal logistic regression model with concentration and time as covariates and subject as a random effect.

Results I: PK model

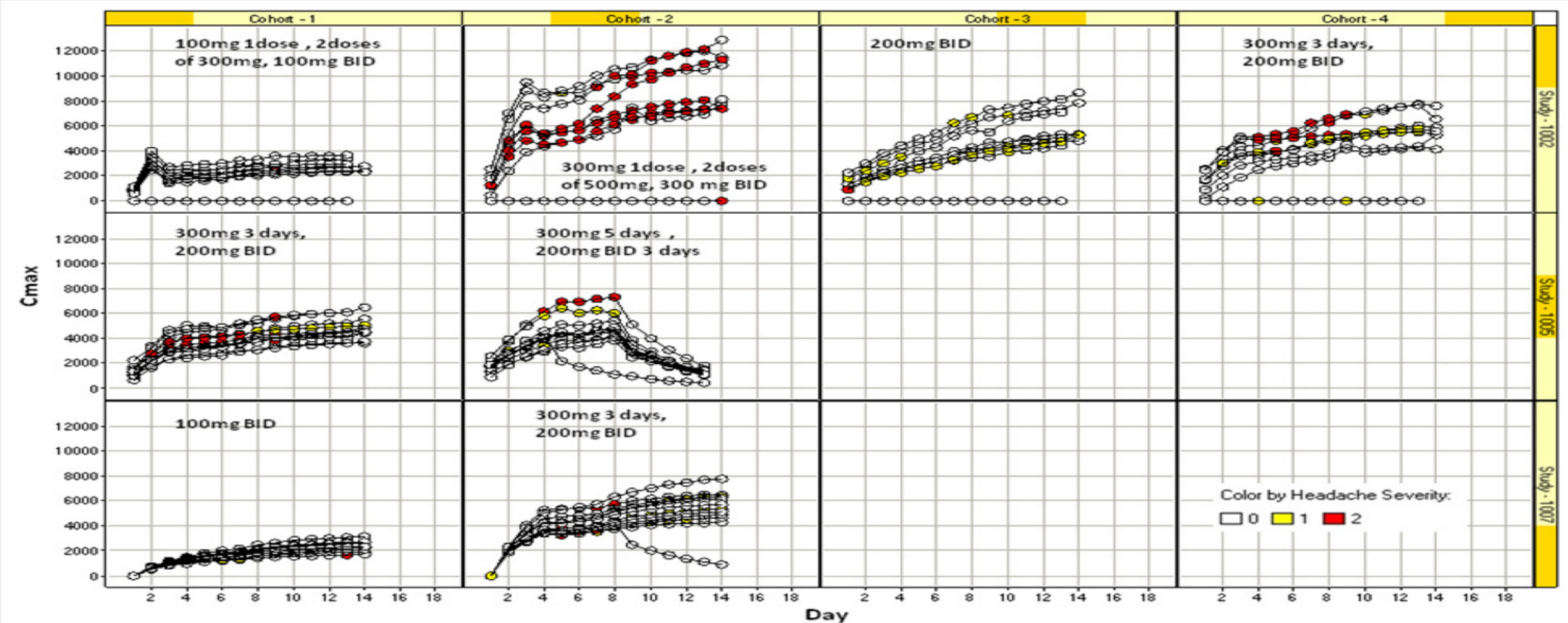
Gut	K_a	Central Compartment V_2/F	Q/F	Peripheral Compartment V_3/F
		CL/F		
Apparent clearance (CL/F),	2.14 L/hr	(21%)		
Apparent central volume of distribution (V2/F),	78.4 L	(41%)		
Apparent peripheral volume of distribution (V3/F),	343 L	(33%)		
Intercompartmental clearance (Q/F),	27 L/hr	(Fixed)		
Absorption rate constant (Ka): at dose up to 700mg with SDD, above 700mg with SDD for SD tablet formulation for the lag time (Alag),	1.29, 0.51 0.68 hr ⁻¹ 0.33 hr	(79%) (45%)		
F after week 1 relative to day 1	0.15	(10%)		

The disposition kinetics were best modelled with 2 compartments with first order absorption rate constant (ka) and a lag-time parameter (Tlag) to characterize the absorption process. Allometric factors on CL/F and Vc were included in the final model. Different ka have been estimated for suspension and tablet and, within suspension, different ka's have been estimated for dose below and above 600mg.



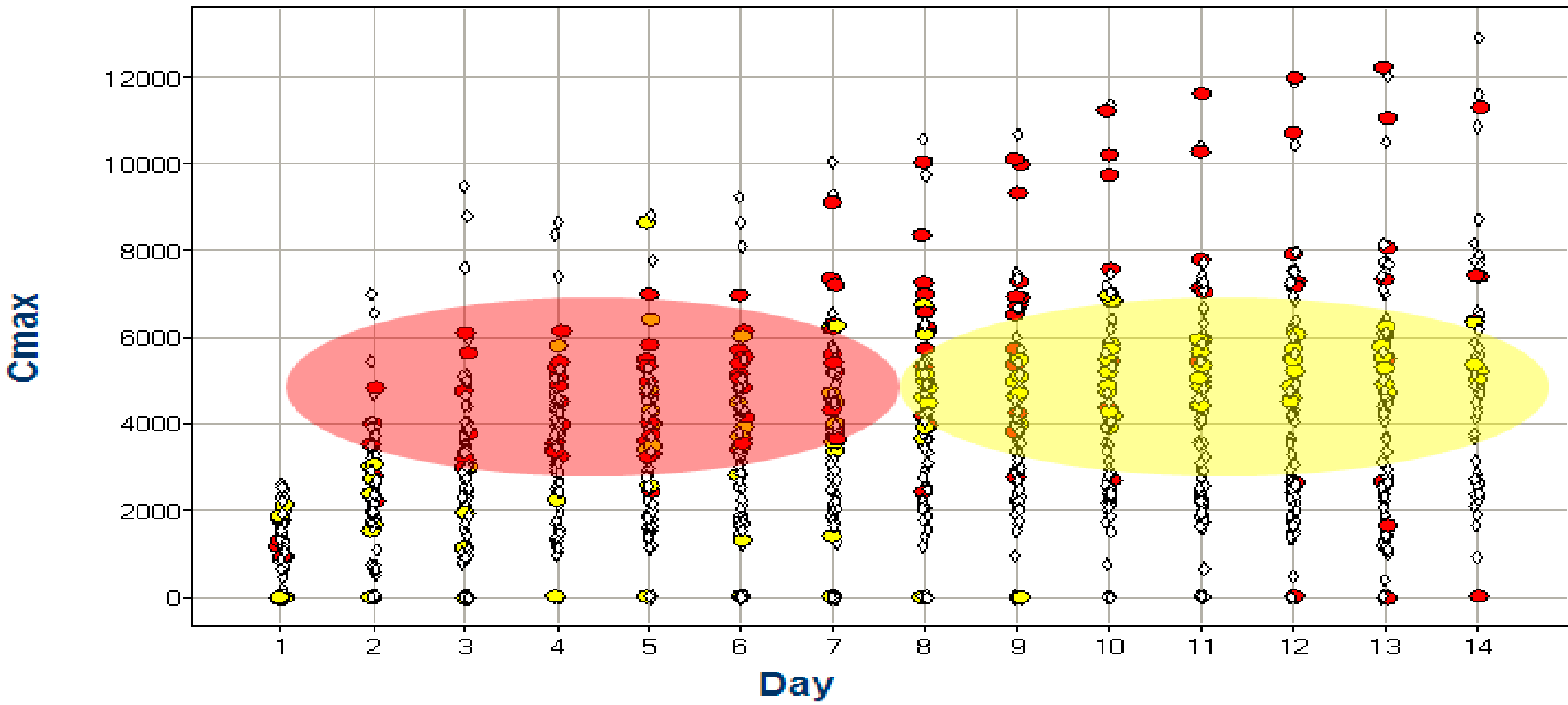
Results II: Visual inspection of Headaches related to PK

The Figure below shows a summary of reported headaches in each of the repeat dose study cohorts related to Cmax achieved on each day.



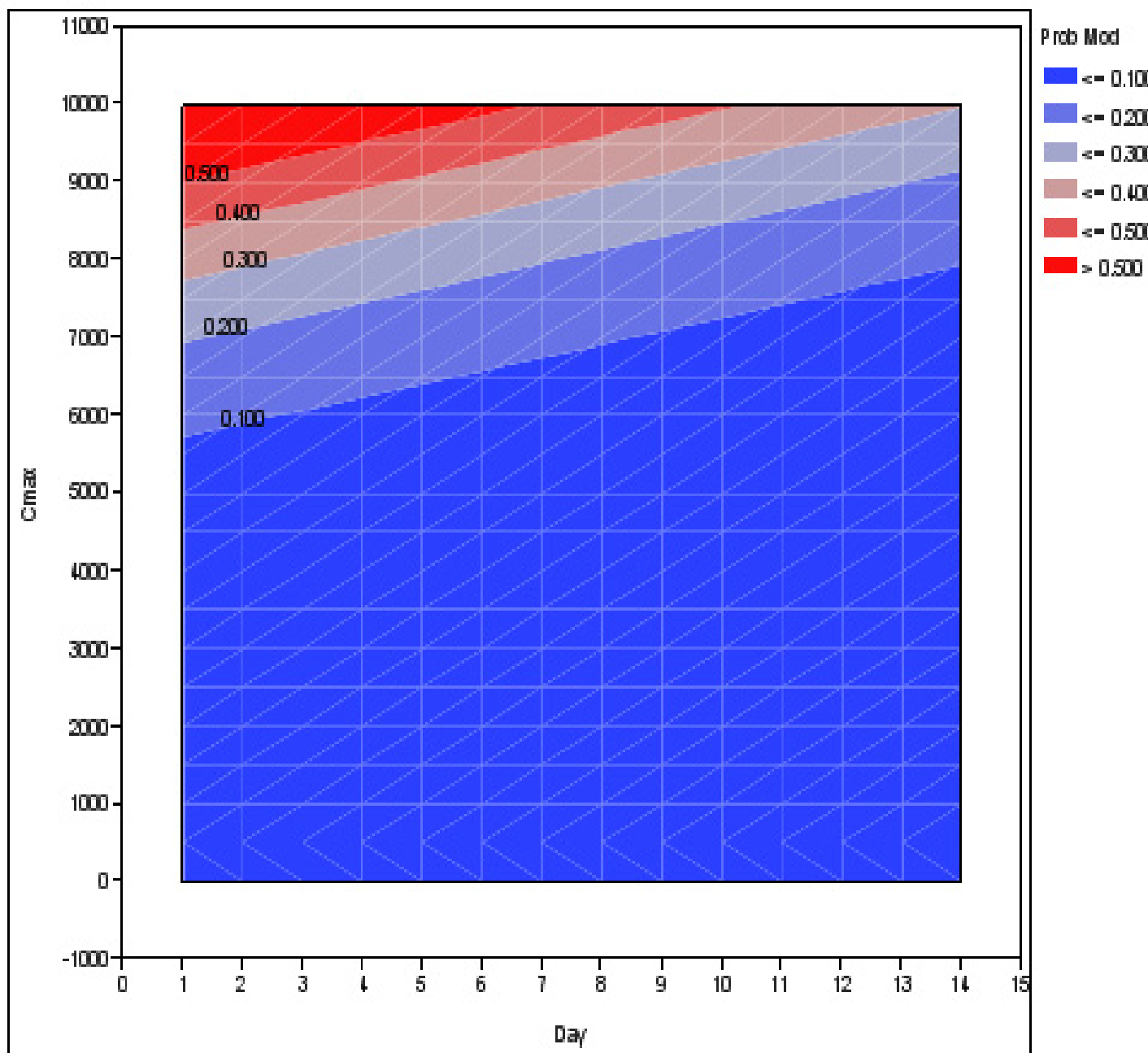
The symbols are coloured by headache severity, with a clear symbol indicating no headache, a yellow symbol indicating a mild headache (did not require rescue medication), and a red symbol indicating a moderate headache (required rescue medication). No cases of headache requiring rescue medication resulting in no pain relief for the study subject occurred. The highest incidence of headaches was reported for Cohort 2 of study 1 (see figure above) where a loading dose of 500 mg BID was followed by a 300 mg BID dose regimen and a high concentration of drug was achieved within the first days of treatment

The Figure below shows the same data overlaid on a single plot. The plot shows that headache incidence and severity are related to both concentration and time. A high concentration given early (e.g. loading dose) was more likely to result in a moderate headache than the same concentration given later.



Results III: PK/PD model

A mixed effects ordinal logistic regression model was used to predict the probability of a moderate headache. Both concentration level and the rate of exposure had statistically significant effects. The model confirmed the visual analysis that the probability of headache increased with concentration but was reduced when concentrations were increased at a slower rate. The contour plot shows the predicted probability of a moderate headache against Cmax and day.



Conclusion

The innovative modelling of the relationship between the headache and pK data has provided an understanding of how to improve tolerability through use of titration. A study is planned to test tolerability to a dosing regimen of 100mg BID (2 days), 200mg BID (3 days), 300mg BID (4 days), followed by 400mgBID maintenance. Figure 4 shows the mean predicted cumulative Cmax against day for the poorly tolerated cohort 2 and the proposed dosing regimen. By the end of week 2, the daily Cmax is similar but the concentration is reached at a slower rate that is predicted to reduce headaches.

