IV-15 Simultaneous ocular adverse event and treatment discontinuation model of pimasertib

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Introduction

Pimasertib is an oral inhibitor of MAPK/ERK kinase (MEK), currently developed for the treatment of pancreatic cancer and melanoma. Observed adverse events (AEs) for this class of drug are mostly skin rash, diarrhea, fatigue, nausea, and visual disturbances including serous retinal detachment and retinal vein occlusion.[1]

Pimasertib was administered to patients with solid tumors and hematological malignancies in two phase I dose-escalation studies. A wide range of pimasertib doses and schedules of administration were tested. All patients were monitored for tolerability (including diarrhea, skin rash, visual disturbances and others). Observations of high variability in terms of time to treatment discontinuation (TD) was found. The present work focuses on ocular AEs (OAEs), AEs limiting pimasertib treatment, and on establishing a TD model. The full model will crucially support the choice of dosing regimen.

Objectives

- Primary objective: identify relationships between exposure and probability of AEs.
- Secondary objectives: explore relationships between exposure and TD, and AEs and TD, although they cannot be addressed separately.
- Develop a joint model correlating pimasertib exposure with OAEs and TD.
- Help decision-making for dosing regimen selection.

Methods

Pharmacokinetics

- A population pharmacokinetic (PK) model with 1, 2 and 3 compartments was investigated. Particular attention was given to potential changes of relative bioavailability across the wide dose range investigated.

Ocular adverse events

- OAEs were graded on a scale from 0 (no AE) to severe, i.e. grade 3 and 4 AEs. A proportional odds model was built for the weekly highest grade OAE observed.
- A Markov first-order component was added to the model to take into account the fact that in two consecutive weeks, the grade of the OAE is most of the time unchanged.
- Exposure effect of pimasertib was represented by weekly area under the concentration-time curve (AUC estimated as weekly dose divided by individual clearance) and maximum concentration (Cmax).
- The logits of the different cumulative probabilities were dependent on AUC accumulating in a KPD compartment with first-order elimination rate constant.[2]
- In addition to the AUC action on the probability of AEs, we assumed that the maximum exposure would also increase the risk of OAEs. Consequently, Cmax was included in the model according to two assumptions: (i) higher Cmax leads to higher risk of OAE over the whole treatment period; or (ii), only during the first month.
- Other covariates tested were dosing schedule (once a day (QD) or twice a day (BID) dosing), potential risk factors for OAEs, such as hypertension history, co-medications (steroids) and demographics.

Treatment discontinuation

- Time to TD may have different origins, the most frequent being treatment discontinuation due to non-efficacy and/or toxicity, patients lost to follow up, and death. In our current analysis, the only available information were AEs and death. Classically we considered the following mechanism for TD and AEs:[3]
  - **Completely at random**: TD and AEs are totally independent
  - **Random**: TD is dependant only on observed AEs and otherwise independent
  - **Informative discontinuation**: TD is dependent on observed and unobserved AEs
- The three different mechanisms lead to three different models that were investigated using the model proposed by Hu et al.[3] Time to TD and OAE were jointly modeled using Weibull hazard with Completely at random, Random, and Informative TD assumptions tested.

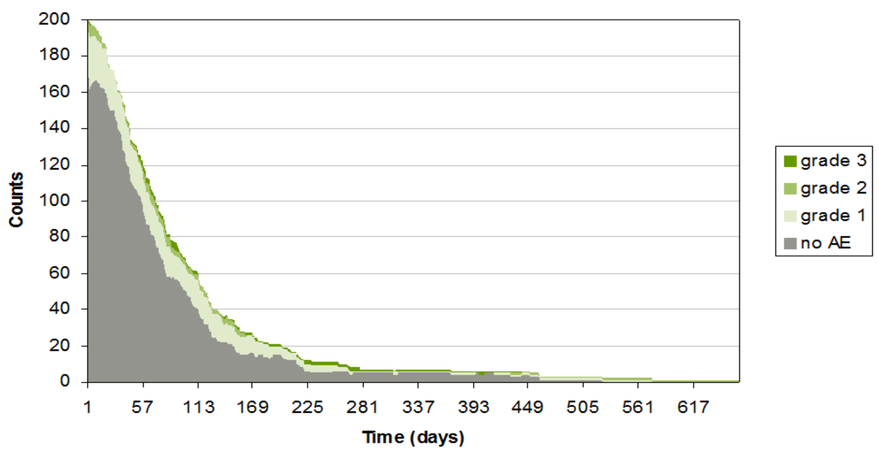
Modeling software

- NONMEM (version VII) with FOCE interaction was used for the population PK model. Bayesian estimates of clearance and Cmax were obtained using the final model. AEs and TD were modeled using NONMEM and Laplacian approximation of the likelihood.

Results

- 199 patients receiving total daily dose ranging from 1 to 255 mg contributed to 4,766 PK, OAEs or TD observations (preliminary data). The cumulative counts for the different grades of OAEs are presented in **Figure 1**. Early appearance of grades 1 and 2 OAEs are clearly shown while grade 3 OAEs appear sparsely after month 2. The plot also clearly establishes the large dropout rate that was observed in the study.

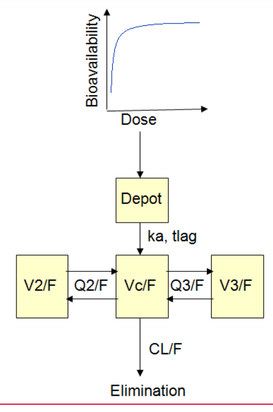
Figure 1. Cumulative number of patients with different grades of ocular adverse event



Population pharmacokinetics

- A three-compartment PK model with first-order absorption and lag time best described the data (**Figure 2**). Relative bioavailability was dependent of dose at low doses and described in a saturated model (**Table 1**). The daily dose producing 50% decrease in relative bioavailability was estimated at 7 mg, limiting this effect to very low doses.

Figure 2. Population PK model



PK, pharmacokinetic

Table 1. Population PK parameters of a three-compartment model with IOV on CL and dose effect on F

Number of patients	199		
Number of observations	4,766		
PK parameter (unit)	**Estimates**	**BSV %**	**BOV %**
Ka (1/h)	6.1	218	
tkag (h)	0.4	0 (fixed)	
CL/F (L/h)	39.3	43	17
Vc/F (L)	200	38	
Q2/F (L/h)	23	74	
V2/F (L)	106	0 (fixed)	
Q3/F (L/h)	4.1	160	
V3/F (L)	1,891	0 (fixed)	
FD50 (mg)	6.9	323	
Residual error (CV%)	43		

Bioavailability (F) modeled as dose/(dose+FD50); BOV, between occasion variability (day 1 versus other days); BSV, between subject variability, given as coefficient of variation; CL, total body clearance; IOV, inter-occasion variability.

Model for ocular adverse events

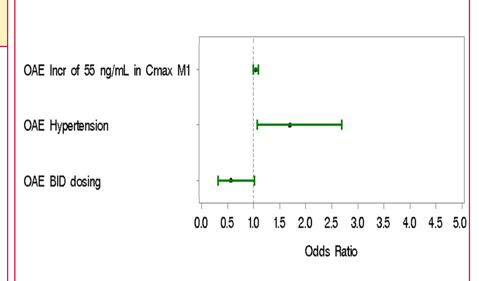
- OAEs were incorporated into the proportional odds model. The different steps of model building are shown in **Table 2**. Markov parameters and AUC mediated through a KPD Emax model were highly significant. BID regimen was associated with a reduction in the probability of OAEs (P(OAE)) while higher Cmax was significantly but transiently increasing P(OAE) in the first month. **Figure 3** shows the odds ratios of the parameters and **Figure 4** shows individual probabilities of AEs versus daily dose at weeks 4 and 12.

Table 2. Different steps of ocular adverse events proportional odds model building

Model	Model description	OF	ΔOF*	p-value
M0	Base model	2527		
M1	**Base Markov model**	**1333**	**1194 (0)**	**<0.001**
M2	**M1 plus Exposure (AUCcum)**	**1204**	**129 (1)**	**<0.001**
M3	**M2 plus BID dosing**	**1199**	**5 (2)**	**0.026**
M4	M3 plus Study	1197	2 (3)	0.128 (ns)
M5	M3 plus Age	1194	5 (3)	0.033
M6	**M3 plus Hypertension (HTA)**	**1195**	**4 (3)**	**0.037**
M7	M3 plus Cmax (whole duration)	1194	5 (3)	0.020
M8	**M3 plus Cmax (month1)**	**1193**	**6 (3)**	**0.019**
Final Model	**Markov model + Exposure + BID dosing + HTA + Cmax (month 1)**	**1189**		

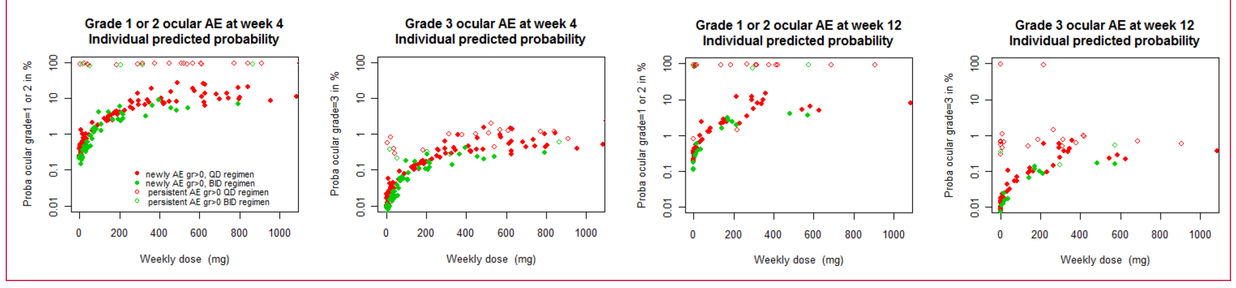
*relative to M#; BID, twice a day. HTA, arterial hypertension.

Figure 3. Odds ratios and 95% CI of parameters for OAE model



CI, confidence interval; OAE, ocular adverse event.
Odds ratios (OR) <1 indicates a protective effect, while OR >1 indicates a worsening effect.

Figure 4. Probabilities of ocular adverse events versus weekly dose at weeks 4 and 12



OAE, ocular adverse event.

Treatment discontinuation

- Neither Random or Informative TD models were successful in terms of model building. A simple model where daily dose was found to explain most of the variability of treatment discontinuation was selected as the final model.

Conclusion

- P(OAEs) are related to higher exposure (AUC and Cmax) with BID found to significantly decrease P(OAE) compared with QD regimen. Presumably, the mechanism of this action is through a reduction of peak concentrations, as indicated by higher P(OAE) linked to higher Cmax during first month of treatment. Diagnosed arterial hypertension was also associated with higher P(OAE). TD rate was found to be dose-related with higher pimasertib doses leading to reduced TD. This suggests a potential treatment benefit for pimasertib, which will be tested further using efficacy data. Model results and simulations will support the choice of dosing regimen in future pimasertib studies.

References

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2. Hénin E, et al. Clin Pharmacol Ther 2009;85:418-25.
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Disclosures

•PG, GM, EA, NR, RAR, AM are employees of Merck Serono SA – Geneva, Switzerland; **BB, CL, OvR** are employees of Merck KGaA, Darmstadt, Germany. *A branch of Merck Serono SA, Coinsins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

Pimasertib is currently under clinical investigation and has not been approved by any regulatory authority. Status: June 2012.