Application of PK/PD Modelling in the Development Eletriptan DR for the Treatment of Acute Migraine and Prevention of Headache Recurrence

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Introduction

- Eletriptan (Relpax®) is a potent, selective, 5-HT1B\1D receptor agonist, which is approved as an immediate release (IR) formulation for the acute treatment of migraine with or without aura.
- Headache recurrence (HR) within the first 24 hours of treatment was found to be 21-23% after treatment with 40-80 mg of eletriptan IR and is a clinically important issue for all migraine treatments[1], occurring in 25-78% of subjects treated with other 5HT1 agonists[2-5].

Objective

- Develop an integrated PK/PD model to describe the relationship between plasma concentration and both Pain Relief (PR) and Headache Recurrence (HR) in patients with acute migraine with the aim of providing:
  - a) A target profile to guide the development of a Dual Release (DR) formulation for the treatment of acute migraine (PR) and prevention of HR.
  - b) Dose response predictions to guide the selection of the optimal IR and MR dose combination for achieving and Sustaining Headache Relief (SHR).

Data

Study	Formulation	Description	n	Doses
1	IR	HV PG PK study	47	10, 30, 60, 90 and 120 mg
2	IR	Patients w/wo Migraine PK study	35	30 mg
3	IR vs CR	HV CO PK study	12	90 mg
4a	IR vs DR(Probe)	HV CO PK study	12	40 mg IR & 40 mg/40 mg DR
4b	IR vs DR(current)	HV CO PK study	12	40 mg IR & 40 mg/40 mg DR
5-10	IR vs P	Patient (General Migraine Pop[n]) PG Efficacy Trial Endpoints: PR & HR 24h	4439	P, 20, 40, or 80 mg IR
11	IR/P vs IR/CR@5h IR/IR@5h	Patient (Enriched-Freq Rec) PG Efficacy Trial Endpoints: PR & HR 24h & 48h	473	P, 40 mg IR, 40 mg CR

Methods

- PK models for IR and CR formulations were established using data from studies 1-3.
- A PK/PD model was developed by simultaneously estimating the joint likelihood of PR and HR across patients receiving placebo, 20, 40 and 80 mg of eletriptan IR (studies 5-10).
- The probability of PR was described by a logistic model, which included a:
  - placebo effect across time
  - baseline effect
  - study effect
  - drug effect (Figure 1).
- The probability of HR at a given time was modelled using a survival model, where the log of the hazard was a function of the probability of PR (Figure 1).
  - Separate parameters for the hazard model were estimated for a general migraine and an enriched patient population (Study 11).

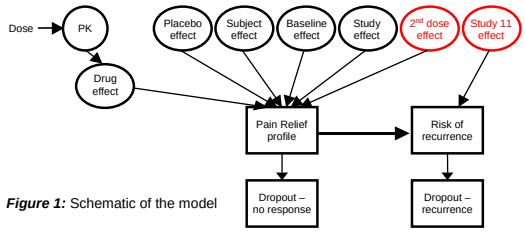


Figure 1: Schematic of the model

Results

Pain Relief, P(Y=1), and Recurrence, P(T>t), models

Model parameters are estimated using nonlinear mixed effects model analysis (NONMEM V)

- Pain Relief Model $g\{P(Y=1)\} = f_p(t) + f_d(C_e) + \eta_Y$
  - Logit transformation $g\{x\} = \log(x/(1-x))$
  - Placebo model $f_p(t) = \beta + A_{pl}\cdot(1-e^{-k_{pl}\cdot t}) + base + Study + A_{pl,2^{nd}\,dose}\cdot(1-e^{-k_{pl}\cdot(t-t_{2^{nd}\,dose})_+})$
  - Drug model $f_d(Ce) = sl\cdot Ce^n$
  - Effect site concentration $Ce(t) = keo\cdot e^{-keo\cdot t} * Cp(t)$
  - Subject specific random effect $\eta \sim N(0,\omega^2)$
- Recurrence Model $P(T>t) = S(t) = \exp(-\int_0^t \lambda(u)du)$
  - Hazard model $\log(\lambda(t)) = hz_i - hz_s\cdot g\{P(Y=1)\}$
- Likelihood $L = \prod_{i=1}^{N}\int P(T,Y\,|\,\eta)P(\eta)d\eta = \prod_{i=1}^{N}\int P(T\,|\,Y,\eta)P(Y\,|\,\eta)P(\eta)d\eta$

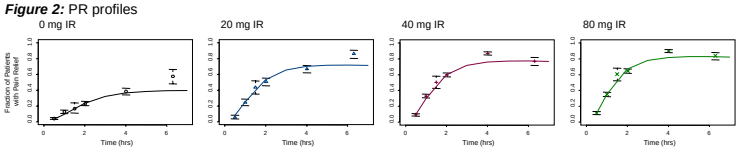
Table 1: Population Parameter estimates from the final pharmacodynamic model

	value	s.e.
A_{pl}	6.92	0.248
k_{pl} (/hr)	0.821	0.0587
$A_{pl,\,2^{nd}\,dose}$	1.27	0.196
β	-7.48	0.305
keo (/hr)	0.447	0.129
n	0.263	0.023
sl	1.04	0.125
hz_i	-2.24	0.0599
hz_s	1.43	0.0547

	value	s.e.
Base = severe	-1.18	0.0878
$hz_{i,\,enriched}$	-1.74	0.12
$hz_{s,\,enriched}$	1.06	0.0738
Study = 6	0.455	0.141
Study = 7	0.155	0.115
Study = 8	0.364	0.151
Study = 9	0.528	0.14
Study = 10	0.663	0.153
Study = 11	0.382	0.185
ω^2	4.81	0.25

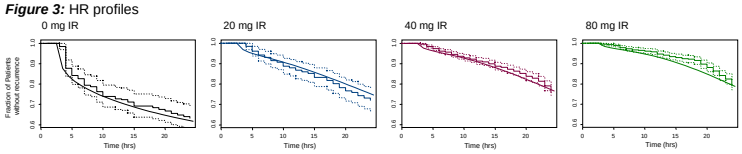
Figure 2 and Figure 3: The model characterises the PR & HR profiles for IR formulation in General Migraine Population (Studies 5-10)

Figure 2: PR profiles



Point & 95% Intervals = Observed data (proportion of subjects with pain relief), solid line = model prediction

Figure 3: HR profiles

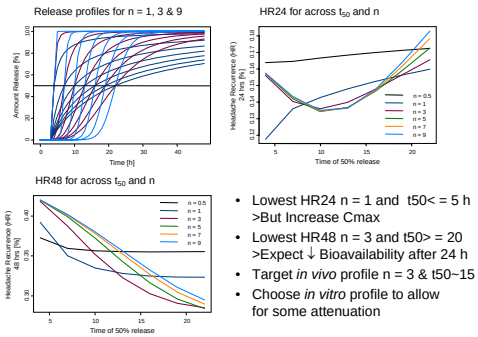


Step function – observed survival (lack of recurrence), dotted line = 95% CI, solid line = model prediction

Simulation (1): Target Profile

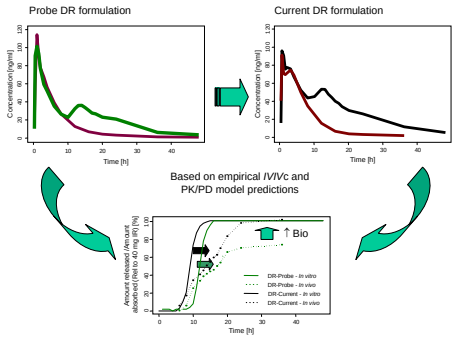
- To aid the development of a DR formulation, simulations were conducted to determine the optimal release characteristics for the MR component of the DR formulation in the prevention of HR. A sigmoidal shape of the cumulative amount released characterizes the properties of the types of formulations being investigated.
- The accumulative amount released ($\int_0^{\infty} I(t)$) (integration of the release rate I(t) over time) can therefore be described by the following equation: $\int_0^{\infty} I(t) = \frac{E_m\cdot(t-tl_2)^n}{(t-tl_2)^n + t_{50}^n}$
- Where
  - Em = maximum amount of the dose released, tl2 = lag before any drug is released, t50 = time to 50% release from the time that release starts (tl2), n = slope factor governing the rate of the sigmoidal release.
  - The observed plasma concentration for the DR formulation CpDR is $Cp_{DR}(t) = I(t) * Cp_{IR}(t) + Cp_{IR}(t)$
- Where Cp(t) is the kinetic profile for the IR release formulation in healthy subjects and migraine patients when migraine free.
- **Figure 6** shows the simulations used to identify the target MR release profile.
  Figure 7 shows the actual PK profiles for the Probe and Current formulation

Figure 6: The impact of changing n and t_{50} on the HR24 and HR48.



- Lowest HR24 n = 1 and t50< = 5 h >But Increase Cmax
- Lowest HR48 n = 3 and t50> = 20 >Expect ↓ Bioavailability after 24 h
- Target *in vivo* profile n = 3 & t50~15
- Choose *in vitro* profile to allow for some attenuation

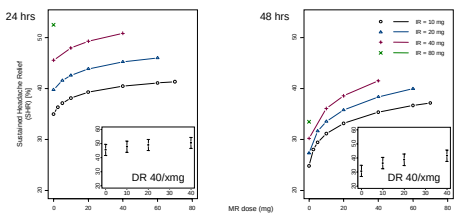
Figure 7: PK and *in vivo/in vitro* release profiles for Probe and Current DR formulations



Simulations(2): Dose Response

- The joint model allowed prediction of the dose response for DR.
- A joint endpoint Sustained Headache Relief (SHR) = PR(2 h)*HR was used to compared possible IR & MR dose.
- 15000 subjects were simulated for each dose combination of the IR and MR components of the DR formulation up to a total dose of 80 mg.
- The impact of model uncertainty was assessed by simulating 158 subjects x 1000 samples from the variance – covariance matrix generated by NONMEM.
- **Figure 8** and **Table 2** show the Dose Response relationship for SHR24 and SHR48 in a general migraine population. Impact of model uncertainty is shown (inset) for the 40/x mg combination.
- For equivalent total daily doses, DR 40/x formulations are expected to provide a larger Sustained Headache Response (SHR) than DR 20/x or 10/x at 24 h e.g. the SHR for 40 mg/40 mg is greater than 20 mg/60 mg and 10 mg/70 mg. This expectation is clear at 48 h.
- The IR component is important since it selects the populations that can prevent from recurring. In essence, the 6.3% absolute difference in the PR(2 h) between 20 mg and 40 mg IR drives the difference in the SHR.
- The simulations indicated that the difference in SHR between DR 40/20 and DR 40/40 at 24 and 48 hours would not be substantial.

Figure 8: Dose response relationship for different IR/MR dose combinations



Conclusion

- On the basis of these simulations it is expected that the optimal 40 mg/40 mg DR formulation will provide a relative reduction in headache recurrence of ~33% in comparison 40 mg IR and an increase in sustained response to 48 hours from 30 to 40%.
- The PK-PD model established using the phase III database for the IR formulation has been used to guide the development and subsequent dose selection for DR formulation being developed for the treatment of acute migraine and prevention of headache recurrence.

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