Model-Based Analysis of a Longitudinal Binary Response as the Primary Analysis for a Phase II Study in Migraine Prophylaxis.

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Introduction

The objective was to design and evaluate a phase II proof of concept/dose-response study in Migraine Prophylaxis, exploiting the characteristics of the primary endpoint optimally and taking into account cost, time efficiency, as well as limiting unnecessary patient exposure to the drug.

The primary endpoint, Migraine Headache Day (MHD), was longitudinal in nature: 1 month of run-in to establish a baseline was followed by 3 months of treatment, and binary: For each patient, every day was either an event or a non-event day.

The objective was addressed by a model-based primary analysis and a two stage design with interim analysis.

Methods

Model

A model describing the placebo time course and drug effect was constructed using literature and in-house historical data. The model had 3 components:

1) a constant and common baseline (BASE) for the probability of an event at a given day prior to treatment,

2) a fractional change in the probability of an event at a given day, expressed as 1-exp(-k*time), which described the expected probability of an event over the 12-week treatment period, and

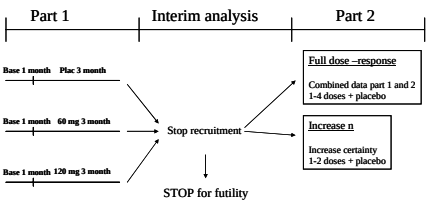
3) 2 parameters which described the modification of the change in probability over time due to placebo treatment effect (PLAC) or active treatment effect (PLAC+MXD).

$$Logit[P(MHD)] = BASE + (1 - \exp(-k * t)) * (PLAC + MXD)$$

Initial Model Parameter Assumptions

Parameter	mean	sd
BASE	6.5 MHD/month (p(MHD)=0.232)	2.8 MHD/month
PLAC	5.2 MHD/month (p(MHD)=0.186)	2.8 MHD/month
MXD (40% vs PLAC)	3.1 MHD/month (p(MHD)=0.111)	2.8 MHD/month
T1/2 (for k)	20 days	9 days

Study Design



Tools

Data analyses were performed using NONMEM (version V).
Simulations and all additional data manipulations and graphics were performed using R (The R Foundation for Statistical Computing, Version 2.1.1 [2005] for Part 1 and Version 2.3.1 [2006] for Part 2)

Design Part 1

More Power with Model based analysis

Sample Size	Power (Type II) To detect 40% vs placebo		Risk (Type I) To continue trial if true effect is 0%
n/group	Model-based analysis (nsim=300)	End of TMT pair-wise comparison	Model-based analysis (nsim=300)
20	81	58	2.3
25	89	67	1.3
30	95	74	1.3
40	98	84	0.1
50	99.9	90	0.3

Interim Analysis

No Drug Effect

Model ID	Description	Objective Function	ΔOF	df	p
22809	BASE	8693.086	114.707	2	<0.001***
22810	BASE + PLAC	8578.379			NA
22811	BASE + PLAC + MXD1	8578.368	−0.011	1	0.916
22813	BASE + PLAC + MXD	8578.176	−0.203	1	0.652
22812	BASE + PLAC + MXD2	8577.959	−0.420	1	0.517
22814	BASE + PLAC + MXD1 + MXD2	8577.937	−0.442	2	0.802

Model Parameters (full model)

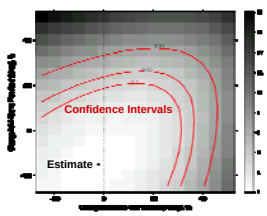
	Parameter estimate	Standard error	95% CI	Population Variability as CV(%)
logit BASE	−1.090	0.052	−1.192, −0.988	25
logit PLAC	−0.597	0.275	−1.136, −0.058	139.1
Half life, log(days)	2.680	0.940	0.838, 4.522	-
logit MaxResp 60mg	0.028	0.296	−0.552, 0.608	-
logit MaxResp 120mg	0.183	0.321	−0.446, 0.812	-

Estimates for Day 70 (full model)

Summary of the Probability of a Migraine Headache Day at Day 70

	Baseline (N=88)	Placebo (N=33)	60mg (N=24)	120mg (N=31)
Probability of a migraine headache day	0.262	0.159	0.163	0.184
95 %CI	0.233, 0.271	0.099, 0.246	0.082, 0.298	0.091, 0.337
Treatment group probability change from baseline (%)	-	36.8	35.4	26.9
95 %CI	-	6.3, 65.3	−6.5, 77.2	-21.1, 74.8
Risk reduction compared to placebo (%)	-	-	2.3	-15.7
95 %CI	-	-	-50.2, 48.6	-79.2, 41.7

40% Drug effect unlikely



Conclusions Interim Analysis

Although the variance on treatment and the size of the placebo response were larger than assumed, the power was still sufficient to define the desired effect size as unlikely.

Design Part 2

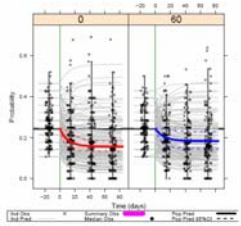
Since a 25% Drug Effect vs Placebo could not be excluded based on the interim analysis, it was decided to continue and power Part 2 to detect this effect. Assumptions were adjusted. In particular both extent and uncertainty of the placebo response were used in the simulations.
A sample size of 120/group had estimated 80% power to detect a 25% Drug Effect vs Placebo. The Type I error was estimated 3.5%.
In addition, only 1 dose (to limit the size of Part 2) was to be studied in women only. Further analysis suggested a larger drug effect in women (majority of target population) than in men, at that dose.
It was decided not to combine Part 1 and 2 data in the final analysis.

Results Part 2

No Drug Effect

Model ID	Description	Objective Function	ΔOF	df	p
810	PLAC	25329.81		2	
811	PLAC + MXD	25326.53	−3.278	1	0.07

Observations and Predictions



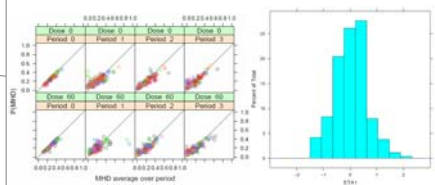
Model Parameters (full model)

	Parameter estimate	Standard error	95% CI	Population Variability as CV(%)
logit PLAC	−0.556	0.099	−0.750, −0.362	129.4
Half life, log(days)	2.130	0.582	0.989, 3.271	-
MXD	0.192	0.103	−0.010, 0.394	-

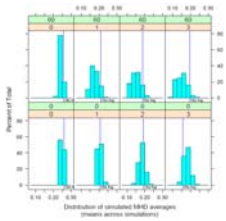
Estimates for Day 70 (full model)

	Baseline (N=264)	Placebo (N=134)	60mg (N=130)
Probability of a migraine headache day	0.248	0.157	0.184
95 %CI	0.236, 0.259	0.133, 0.185	0.146, 0.230
Treatment group probability change from baseline (%)	-	36.8	25.9
95 %CI	-	46.4, 25.7	41.3, 7.5
Risk reduction compared to placebo (%)	-	-	-17.2
95 %CI	-	-	-36.4, 2

Model Diagnostics



Posterior Predictive Check



Conclusions

- Model-based analysis allowed for much smaller sample sizes (about half the subjects)
- Two-stage design allowed for adjustments in design during trial and stopping early if appropriate (time and money).
- Intuitive outcome: Probability of having a Migraine Headache Day

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