Final report - Dose response project

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1.Introduction

In the drug develop procedure, pharmaceutical companies are required to conduct rigorous clinical trails to evaluate and test the new drug before they make further investment. The goal of these clinical trials is to investigate whether the new drug is safe for humans, to explore the efficacy and feasibility, and to decide what is the most appropriate dose. Clinical trials are usually divided to 5 phases: pre-clinical trail, Phase I clinical trial, Phase II clinical trail, Phase III clinical trial, and Phase IV clinical trail. Among them, Pre-clinical trail contains the drug discovery experimentation in vitro studies, PhaseI clinical trial is the screening test for safety, Phase II clinical trial is to decide the efficacy and feasibility in a small group of people, Phase III clinical trial is the comparative efficacy trial to test with larger group of people (1,000 - 3,000) and Phase IV clinical trail is the post-marketing surveillance. During this procedure, selecting the optimal dose is a key step because a high dose may lead to a high toxicity while a low dose may fail to provide sufficient evidence to show the efficacy of this drug [1]. In order to prevent the potential risk like the patients would be exposed to the side effects, statisticians play a vital role in ensuring the design is blinded and the data are analyzed objectively [2]. Statisticians need to submit their analysis plan about how they are going to analyze the data in each specific trail before they see the results [2].

However, in the early stage, the sample size is small, and little is known about the data, statisticians would find it is difficult to make a decision in their statistical research plan. It is hard for them to select the best model when they cannot foresee what kind of data they will face. Therefore, in order to decrease the effects from the uncertainty, Novartis Company developed a method —"multiple comparisons and modeling", which is called MCP-Mod for short, to help statisticians to target on several candidate models that could fit the observed data. Recently, European medicine agency admitted this method to be efficient in phase II trail, which is the first trails to affect patients to identify whether the drug is effective and lock onto several efficacious doses [2]. A clinical trail of a new drug to reduce pain for migraine patients conducted by Merck company is a presentative example to show how MCP-mod methods work.

In 2010, Merck company developed a new drug MK-3207 for acute migraine. As a member of calcitonin gene-related peptide (CGRP) receptors which are convinced to be useful in the acute treatment of migraine, MK-3207 was hypothesized to have greater efficacy based on its features of being rapidly absorbed and the results in radioligand binding and cell-based functional assays [3]. To evaluate MK-3207, Merck designed a randomized controlled trail to implement the dose selection employed the MCP-Mod method. They recruited 517 patients into eight groups to accept different doses, and collected the data of successful outcomes. After the statical analyses, the researchers found MK-3207 has side effects on liver. As a result, although this drug is effective to treat migraine, Merck stopped the investigation. In this current project, our goal is to get familiar with this dose selection method and to conduct a replicated study of a drug discovery experimentation designed by Merck to treat the migraine. In our project, we followed their dose response selection steps to fit the several alternative models and use three criteria to assess the features of each model. After that, the best model were selected to calculate the effective doses and the minimum effect dose.

2. Study design

The Merck's Phase II trial was randomized, double-blind, parallel-group study and placebo controlled. Throughout the trial, the placebo rate was 25 percent. In addition, the trial was also a multicenter trial, which was conducted at 47 sites in the United States (19 sites), Canada (9 sites) and Europe (19 sites)

between July 2008 and January 2009. Moreover, the study was performed in a two-stage adaptive design, with two interim efficacy analyses, was employed to facilitate optimal dose selection. The first interim efficacy analysis was performed aimed to drop the less-effective dose levels from further randomization in Stage 2. The second interim efficacy analysis was performed in order to test for futility and potentially to add a dose group at either the low or high end of the dose range. The whole study contained 517 patients divided into 8 groups: placebo, 2.5, 5, 10, 20, 50, 100 or 200 mg of the new drug. Then they measured how many patients were free of pain 2 hours after taking the drug in each group. The results are shown in the following Figure 1.The 517 patients were divided into two stages.

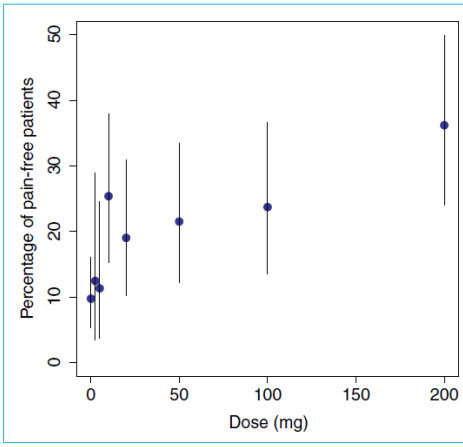


FIGURE 1 The results from Merck's trial on a drug to treat migraine. Dose groups included 133, 32, 44, 63, 63, 65, 59 and 58 patients, respectively. Vertical bars present 95% confidence intervals

2.1. Two stages

2.1.1. Stage 1

In stage 1, 312 patients were to be randomized to receive a single dose of MK-3207 2.5, 5, 10, 20, 50, or 100mg (N=39 for each dose), or matching placebo for each dose (total N =78) in a double-dummy design. Therefore, there were several possible sets: two active tablets; two placebo tablets; one placebo and one active tablet; all patients took the same number of tablets of each size. The patients were stratified according to their self-reported retrospective usual migraine response to a triptan with a 75 percent cutline. The first interim analysis was performed after 312 patients had been randomized and a minimum of 20 patients had been treated in each of the three-lowest MK-3207 dose groups. The lowest MK-3207 group ("dose S"), which was the lowest identified promising dose, up to 20 mg, was identified. Then the "poor dose response" test was performed aimed to increase the likelihood of observe a dose-response relationship from the study. If the two-hour pain-free response rate at any of the doses below "dose S" was at least 10 percentage points below the next-lower dose, all doses were to be continued into Stage 2. However, if a poor dose response was not identified, the MK-3207 dose below the lowest effective dose and higher doses were to be continued into Stage 2.

2.1.1. Stage 2

In stage 2 the remaining 240 patients were to be randomly allocated to the MK-3207 dose levels (MK-3207 or placebo). For each dose below dose S, 18 patients were enrolled as well as six patients to each of the matching placebo groups. The remaining patients were equally allocated to the remaining higher doses. The randomization ratio of active MK-3207 to placebo remained at 3 : 1. The second interim analysis was performed when a minimum of 40 patients were treated in each of the three highest dose groups, or a total of 460 patients had been randomized in the trial, which ever occurred first. The purpose was to determine whether a higher (200 mg) or lower (1 mg) dose of MK-3207 should be added:1)assessment of futility, to determine whether the three top doses (20, 50, 100 mg) had suboptimal efficacy (thereby indicating a need to add the 200-mg arm to attempt to identify an effective dose); 2) assessment of dose response and evaluation of a lack of sufficient separation of the lowest and highest doses on efficacy (thereby indicating a need to add the 1-mg arm to attempt to identify a minimally effective dose).

2.2. Procedure

Patients who had moderate or severe migraine headache were enrolled and provided with MK-3207 or placebo to be taken as soon as they experienced a headache. They were instructed not to treat with their own rescue medication until after their two-hour pain assessment. If they were still experiencing a moderate or severe headache at two hours following initial treatment, they could take their own rescue medication. At the same time, the patients were required to record subjective assessments of pain severity, associated migraine symptoms and other measures at specified time intervals in a migraine diary. Besides, the adverse events were also important to record. After that, patients should return to the study site about five to seven days after treatment in order to allow review of their diary, assessment of medication compliance, and tolerability and safety monitoring.

2.3. Assessment

The headache severity was assessed using a four-grade scale: no pain, mild pain, moderate pain and severe pain at baseline (0 hour—time of taking study medication) and at 0.5, 1, 1.5, 2, 2.5 dosage 24 and 48 hours post-dose. The adverse events were also recorded at the same time points as the headache severity ratings. Tolerability and safety were assessed via spontaneous adverse event reports and routine pre and post-study physical and laboratory examinations, electrocardiograms (ECG), and vital signs.

2.4. Statistical analysis

The primary efficacy variable was the percentage of patients reporting pain free after taking study medicine two hours later. Other five secondary efficacy endpoints including pain relief, absence of photophobia at two hours, absence of phonophobia at two hours, absence of nausea at two hours and 2-24 hour sustained pain free without use of rescue medication. The primary hypothesis was that there was a positive response trend across MK-3207 doses, when measured by the proportion of patients who were pain free two hours post dose. The analyses were performed using GLM function with categorical terms for baseline headache severity, stratum (usual triptan response) and geographic region, with treatment group. Age was also included as continuous covariate. In this study, the null hypothesis was that all dose responses are the same as placebo with a response rate of 10 percent. The alternative hypothesis was that the response rates were between 10 and 30 percent.

3. Method

3.1. Models

The models that we fitted in the project are as follows:

Emax $= f(d,\theta) = E_0 + E_{max}\frac{d}{ED_{50}+d}$

- ED_{50} : Dose giving half of the asymptotic maximum effect

Exponential $= f(d,\theta) = E_0 + E_1(exp(d/\delta) - 1)$

- This model is intended to capture a possible sub-linear or a convex dose-response relationship.
- δ parameter, controlling the convexity of the model.

Quadratic $= f(d,\theta) = E_0 + \beta_1 d + \beta_2 d^2$

- This model is intended to capture a possible non-monotonic dose-response relationship.
- β_2 parameter controls whether model is convex or concave.

Logistic $= f(d,\theta) = E_0 + E_{max}/\{1 + exp[(ED_{50} - d)/\delta]\}$

- δ : Parameter controlling determining the steepness of the curve.

3.2. Multiple comparisons and Modeling Techniques : MCP-mod

1. **Choose a set of candidate models M**

   - A set M of candidate models covering a suitable range of dose response shapes. Also, unrealistic pattern that describes the data needs to be excluded.

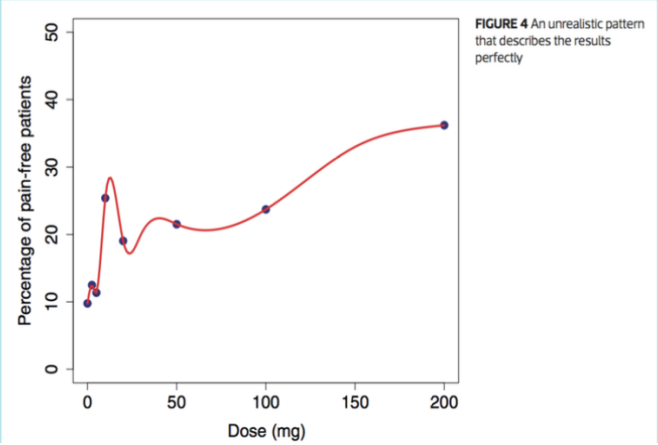


FIGURE 4 An unrealistic pattern that describes the results perfectly

2. **Choose best the contrast coefficients to maximize the power of detecting the m-th model.**

$$H_0^m : c_m'\mu = 0 \quad v.s. \quad H_1^m : c_m'\mu > 0$$

$$T_m = \frac{c_m\bar{Y}}{\sqrt{S^2\sum_{i=1}^{k} c_{m_i^2}/n_i}}$$

   C_{m_i} : Every single contrast test is to determine whether the given dose response shape is statistically significant.

3. **Combining the test statistics T_m into a single decision rule is to take the maximum.**

$$T_m = max_m T_m \ (min_m P_m < \alpha)$$

4. **Fitting the selected model to the data and estimating adequacy**

$$MED = argmin_{d\in(d_1,d_k]}\{f(d,\theta) > f(d_1,\theta) + \Delta\}$$
$$TD_\Delta = min\{x|f(x) > f(0) + \Delta\}$$

   Δ denote the clinically relevant difference (A dose better than placebo). The smallest dose which shows a clinically relevant and a statistically significant effect. TD is similar to the usual definition of the minimum effective dose(MED).

$$ED_p = min\{x|f(x) > f(0) + p(f(d_{max}) - f(0)\}$$

   The ED(effective dose) is defined as the dose that achieves a certain percentage p of the full effect size(within the observed dose-range) over placebo.

3.3. Details about step 2 and step 3

3.3.1 Choose the optimal contrasts

Assume that

$$Y_{ij} = \mu_i + \epsilon_{ij}, \quad \epsilon_{ij} \sim N(0, \sigma^2)$$

where $\mu_i = f(d_i, \theta)$ are the unknown treatment means with $\mu = (\mu_1, \cdots, \mu_k)$. Let $\bar{Y}_i = \sum_{j=1}^{n_i} Y_{ij}/n_i$ denote the arithmetic mean of group i with $\bar{Y}' = (\bar{Y}_1, \cdots, \bar{Y}_k)$. Let further $S^2 = \sum_{i=1}^{k}\sum_{j=1}^{n_i}(Y_{ij} - \bar{Y}_i)^2/v$ denote the pooled variance estimator with $v = \sum_i n_i - k$ degrees of freedom. Our goal is to select the

best fitting models out of the candidate set M, while controlling the FWER. To this end, we test the null hypotheses

$$H_0^m : c'_m\mu = 0 \;\; v.s. \;\; H_1^m : c'_m\mu > 0$$

For given $k \times 1$ contrast vectors $c'_m = (c_{m1}, \cdots, c_{mk})$ of known constants subject to $c'm1 = 0, m = 1, \cdots, M$. This leads to the single contrast tests

$$T_m = \frac{c_m\bar{Y}}{\sqrt{S^2 \sum_{i=1}^k c_{m_i^2}/n_i}}, \;\; m = 1, \cdots, M.$$

Under the assumptions of model (1) and H_0^m, each test statistic T_m has a central t-distribution with v degrees of freedom. When H_0^m is not true, T_m follows a noncentral t-distribution with noncentrality parameter $\gamma_m = c'_m\mu/(\sigma^2 \sum_{i=1}^k c_{mi}^2/n_i)^{\frac{1}{2}}$. We consider the problem of determining the "best" contrast associated with a given model function $f(d, \theta)$, in the sense that, when that model is correct, it maximizes the chance of rejecting the associated null hypothesis. That is it maximizes the noncentrality parameter $\gamma = \gamma(c)$. One should choose $c_{opt}(f)$ such that

$$c_{opt}(f) = argmax_c g(c, \mu)$$
$$g(c, \mu) = \frac{(c'\mu)^2}{\sum_{i=1}^k c_i^2/n_i} = \sigma^2[\gamma(c)]$$

It can be shown that these optimal contrast coefficients do not depend on the full parameter vector θ_m of the model, but only the parameters in its standardized model function θ_m, which determine the model shape (see Bretz et al. 2005) and the group sample sizes.

Letting $(\mu_{m1}^0, \cdots, \mu_{m1}^k)^T = (f_m^0(d_1, \theta_m^*), \cdots, f_m^0(d_k, \theta_m^*),)^T$. Assuming that there exists a standardized version f^0 of f such that $\mu = \mu(f) = \theta_0 + \theta_1\mu(f^0) = \theta_0 + \theta_1\mu^0$, it is easy to verify that $c'\mu = \theta_1 c'\mu^0$ and $g(c, \mu) = \theta_1^2 g(c, \mu^0)$. Therefore, $c_{opt}(f) = c_{opt}(f^0)$ and it suffices to consider the problem of finding the c_{opt} corresponding to the standardized model f^0.

[Balanced sample size]

Under balanced sample size allocation $n_i = n, i = 1, \cdots k$ and under the restriction $||c||_2 = 1$, $g(c, \mu) = n(c'\mu)^2$. It suffices to maximize $(c'\mu)^2$ in c. It follows from the Cauchy-Schwarz inequality and our assumptions on c that $(c'\mu)^2 = [c'(\mu - \bar{\mu}1)]^2 \leq ||\mu - \bar{\mu}1||^2$, where $\bar{\mu} = \mu'1/k$.

$$c_{opt} = \frac{\mu - \bar{\mu}1}{||\mu - \bar{\mu}1||} = \frac{\mu^0 - \bar{\mu^0}1}{||\mu^0 - \bar{\mu^0}1||}$$

Since $c' \frac{(\mu - \bar{\mu}1)}{||\mu - \bar{\mu}1||} = 1$ and $cc' = 1(||c||_2 = 1)$.

[Unbalanced sample size]-MK's data case (Answer for Dr.Wu)

In unequal sample sizes per treatment arm, c_{opt} cannot be expressed in closed form and numerical optimization techniques are required. By assumption, $c'1 = 0$ and $||c|| = 1$, so that c can be expressed as a function of $k-2$ free parameters δ, that is $c = h(\delta)$ for some parameterization function h. For numerical optimization purposes, it is often easier, more stable, and more robust to use a parameterization h for which the elements of δ are unconstrained. In the following we describe one possible choice for h, based on a spherical parameterization. Because c takes values on the surface of the unit sphere in R^k, its elements can be expressed in spherical coordinates as,

$$c_i = sin(\gamma_i) \prod_{j<i} cos(\gamma_j) \;\; i = 1, \cdots k-1$$
$$c_k = \prod_{j<k} cos(\gamma_j)$$

for a set of angles $\gamma_1, \cdots, \gamma_{k-1} \in (-\pi/2, \pi/2)$. **Note that we have reduced the number of parameters by 1 because the condition $||c|| = 1$ is satisfied in the above equation.** The second restriction $c'1 = 0$ is established by noting that $c_1 = sin(\gamma_1) = -\sum_{i>1} c_i = -cos(\gamma_1)\sum_{i>1} c_i^1$, where $c_i^1 = c_i/cos(\gamma_1)$. It then follows that $\gamma_1 = tan^{-1}(-\sum_{i>1} c_i^1)$, so that we only require the angles $\gamma_2, \cdots \gamma_{k-1}$. These are free, but constrained to the box $(-\pi/2, \pi/2)^{k-2}$. **We obtain an unconstrained parameterization by defining $\delta_i = log(\pi/2 + \gamma_i/\pi/2 - \gamma_i)$ or, equivalently, $\gamma_i = -\pi/2 + \pi/(1 + exp(-\delta_i))$. This parameterization can be used to obtain the optimum contrast c_{opt} using standard optimization software.**

3.3.2. Model Selection Procedure based on T_m

Once we have optimal contrast coefficients for each model in M, we evaluate the significance of the individual models in terms of the corresponding single contrast tests T_m. Each Tm translates into a decision procedure, whether a selected dose response curve $f_m(d, \theta)$ is significant given the current data,while controlling the FWER at level α. A good candidate curve is chosen as one with a significant contrast test, given that its individual multiplicity adjusted P-value is less than α. If we do not obtain a significant contrast test, no model is selected from the set M, and the modeling component of the MCP-Mod procedure is not undertaken.

Possible statistical non significance reasons: small sample sizes, high variance, the set M might have been poorly chosen so that the candidate models do not fit the true curve.

If at least one model is significant, a reference set of good models is obtained. Each model in the reference set is then statistically significant at FWER α and approximates the true model satisfactorily. The true model should be associated with the minimum P-value by construction of the MCP-Mod method. In practice, it might be hard to decide upon the best model. If the second-best model has a P-value lying close to the minimum P, both models might be worth later consideration. In this case, additional data acquisition or further decision elements might be required.

Fitting the model with the highest T-value (or equivalently, min P-value) is not possible because of numerical instabilities. The recommended procedure is to progress through the "ordered" reference set until model convergence is achieved or the reference set is exhausted. Alternative procedure is to order the reference set by an appropriate information criterion. Details on fitting the models and estimating the parameters are given in Bates and Watts (1988) and Pinheiro and Bates (2000). The following is regarding several different criteria in choosing best model.

1. **AIC: Selects model with smallest AIC.**
2. **maxT**: Selects the model corresponding to the largest t-statistic while controlling the FWER.

$$T_m = \frac{c_m \bar{Y}}{\sqrt{S^2 \sum_{i=1}^{k} c_{m_i^2}/n_i}}$$

   - If the true dose-response shape coincides with μ_m^0 for some m, T_m would be the most powerful test among all contrast tests to detect the particular dose-response shape.

3. **aveAIC**: Uses a weighted average of the models corresponding to the significant contrasts. The model weights are chosen by the formula: $w_i = exp(-0.5AIC_i)/\sum_i(exp(-0.5AIC_i))$

4. Results

4.1 MCPMod Results

In this section, we will show the MCPMod result for migraine case. The whole method procedure has been demonstrated in 3.2, and the corresponding results are as following as the same order.

Step 1: Choose a set of candidate models M The set of candidate M contains five models: Quadratic, Logistic, Emax, Exponential, and BetaMod.

Step 2 & **Step 3**: Choose best the contrast coefficients to maximize the power of detecting the m-th model. Combining the test statistics T_m into a single decision rule is to take the maximum.

Contrast coefficients generation and the following maximization are mainly calculated by R package "DoseFinding", and the decided Tm are as below. BetaMod is not significant in this case, so this model is excluded from candidate set in the following step. Now, we have four models for consideration. There

Model	quadratic	logistic	emax	exponential	betaMod
T-statistics	3.759	3.742	3.726	3.657	0.473

are some common criteria to select best model based on our dataset. Either AIC, aveAIC, and maxT can be criteria to select one optimal model from candidates. In general, if the pattern of response points

Criteria	Emax	quadratic	exponential	logistic
AIC	11.45	13.83	14.59	15.95
maxT	3.73	3.76	3.66	3.74
aveAIC	0.62	0.19	0.13	0.07

are clear, the selected model should be consistent across all criteria. However, it is not the case in our study. The table shows the score of four candidate models on AIC, aveAIC, and maxT.

We can see that max_T gives different suggestion from the other two criteria. Under this kind of situation, it is necessary to remain both Emax and Quadratic model for consideration. Also, it also indicates that the pattern of dose-response results may not as clear as expected because of the nonconsistency of model selection.

Step 4: Fitting the selected model to the data and estimating adequacy

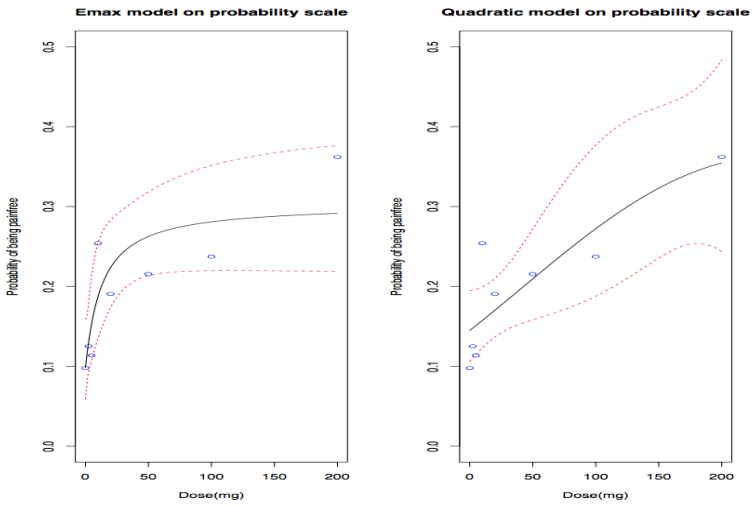
The following tables shows the results of TD (target dose) and ED (effective dose) on Emax model and Quadratic model.

	TD	Δ	Dose type
Emax	5mg	0.3	discrete
Quadratic	200mg	0.3	discrete
Emax	4.05mg	0.3	continuous
Quadratic	122.18mg	0.3	continuous
Emax	2.5mg	0.2	discrete
Quadratic	100mg	0.2	discrete
Emax	1.37mg	0.2	continuous
Quadratic	71.57mg	0.2	continuous
Weighted average TD	17.60mg	0.3	
Weighted average TD	11.67mg	0.2	

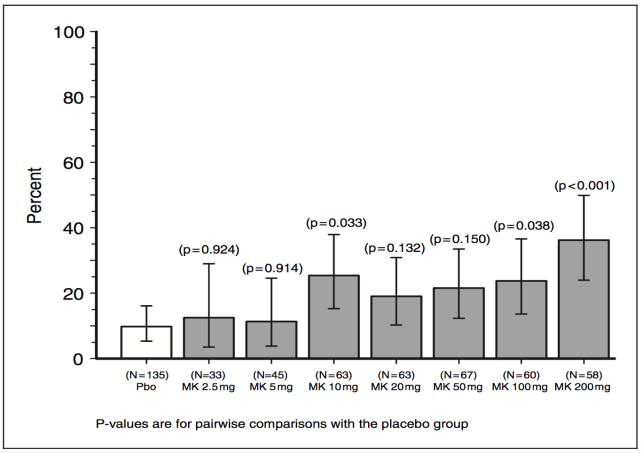
	ED	p	Dose type
Emax	2.5mg	0.5	discrete
Quadratic	100mg	0.5	discrete
Emax	1.37mg	0.5	continuous
Quadratic	68.75mg	0.5	continuous
Emax	2.5mg	0.4	discrete
Quadratic	100mg	0.4	discrete
Emax	0.91mg	0.4	continuous
Quadratic	53.01mg	0.4	continuous

4.2 The efficacy result - model curve and indication

Fit curve in Emax model and Quadratic model. We can see 95% confident interval in Emax model can include all points, but Quadratic model looks more linear. It seems that Emax model is more reasonable because of CI, but it is hard to tell if 10-mg dose is just by random. 10-mg dose is suddenly more effective than 5-mg dose, and obviously more effective that next three doses.



This figure from the clinical trial report paper is based on the model adjusting for baseline headache severity, geographic region, age and usual triptan response, which information are not feasible for us. The provided confident interval for each dose were overlapping, and it is not possible to definitively conclude that the 200-mg dose was more effective than other doses from 10 mg and up. It is possible that the apparent greater efficacy of the 200-mg dose was a chance finding.



4.3 The safety result

The figure from the clinical trial report paper shows the number of patients with adverse events within 14 days post-dose. The report rate of patients with one or more adverse events in each dose group is around 25% to 30%, which is not an ideal number. Moreover, in extended Phase 1 clinical pharmacology studies of MK-3207, some subjects experienced delayed liver-test abnormalities, generally following discontinuation of drug administration. Based on these information, it was decided to discontinue MK-3207 clinical trial to phase 3.

	Placebo (*N* = 142)	MK-3207 2.5 mg (*N* = 32)	MK-3207 5 mg (*N* = 47)	MK-3207 10 mg (*N* = 66)	MK-3207 20 mg (*N* = 67)	MK-3207 50 mg (*N* = 68)	MK-3207 100 mg (*N* = 62)	MK-3207 200 mg (*N* = 63)
Patients with:								
One or more adverse event	29 (20.4)	10 (31.3)	18 (38.3)	17 (25.8)	18 (26.9)	18 (26.5)	19 (30.6)	17 (27.0)
Drug-related[‡] adverse events	14 (9.9)	6 (18.8)	11 (23.4)	7 (10.6)	12 (17.9)	15 (22.1)	10 (16.1)	9 (14.3)
Serious adverse events	1 (0.7)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Triptan-related adverse events[§]	2 (1.4)	2 (6.3)	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	2 (3.2)
Most common adverse events*								
Dry mouth	3 (2.1)	0 (0.0)	3 (6.4)	1 (1.5)	2 (3.0)	4 (5.9)	0 (0.0)	1 (1.6)
Nausea	5 (3.5)	1 (3.1)	2 (4.3)	3 (4.5)	5 (7.5)	3 (4.4)	5 (8.1)	2 (3.2)
Vomiting	0 (0.0)	0 (0.0)	3 (6.4)	1 (1.5)	1 (1.5)	0 (0.0)	1 (1.6)	1 (1.6)
Fatigue	4 (2.8)	1 (3.1)	2 (4.3)	2 (3.0)	2 (3.0)	4 (5.9)	0 (0.0)	2 (3.2)
Dizziness	2 (1.4)	3 (9.4)	4 (8.5)	2 (3.0)	2 (3.0)	2 (2.9)	1 (1.6)	2 (3.2)
Headache	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	3 (4.8)	0 (0.0)

N = patients who took at least one tablet of the study medication; placebo is the pooled arm of all matching placebo doses.
[‡]As determined by the investigator.
[§]Triptan-related adverse events include chest pain, chest tightness, throat tightness, asthenia, paresthesia, dysesthesia or hyperesthesia
*Incidence ≥5% in one or more treatment groups.

5. Conclusion

This course project provides valuable opportunity for us to study much more about the function of clinical trial, especially in phase 2. MCPMod is a practical method for finding trend to make decision based on limited information. It helps select the best model and then we can estimate the dose response rate where beyond the proposed doses. In the MK-3207 case, we met the problem that not able to find the only best model. Emax model and Quadratic model are selected by different criteria, which is not usual but happens reasonably when pattern of response points is ambiguous. This situation leads to the uncertain determinant whether the drug is effective enough or not. The main goal of clinical trial phase 2 is to assess efficacy of drug, and also keep evaluating the safety by larger patient number. Combining the MCPMod results and the safety issue, it meets our expectation that MK-3207 was not developed further. The clinical trial stopped at phase 2.

Reference

1.Bretz, F., Pinheiro, J. C. and Branson, M. (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics, 61(3), 738–748.

2. Baayen, Corine. "The drugs don't work... or do they?." Significance 13.4 (2016): 38-41.

3. Hewitt, D. J., Aurora, S. K., Dodick, D. W. et al. (2011) Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia, 31(6), 712–722.