Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine

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Background

- This study evaluated the CGRP receptor antagonist MK-3207 for acute treatment of migraine
- The objective of this dose-find- ing study was primarily to characterize the dose response of oral MK-3207 over a range of doses for the acute treatment of migraine and to identify effective doses for further study in pivotal efficacy trials.
- The study used an adaptive design to efficiently assess a broad range of doses.

Introduction

- Calcitonin gene-related peptide (CGRP)
  - neuropeptide that has a key role in the pathophysiology of migraine
  - CGRP receptor antagonists olcege- pant (given intravenously) and telcagepant (given orally) have been demonstrated to be effective and generally well tolerated in the acute treatment of migraine
- MK3207
  - new, highly selective CGRP receptor antagonist, rapidly absorbed
  - It was hypothesized that the higher potency of MK-3207 might lead to greater efficacy relative to telcagepant and existing oral triptan treatments.

Method

- i.Patients
  - Age: 16-85; Had greater than one year history of migraine that typically lasted 4–72 hours if untreated.
  - Had two to eight moderate or severe migraine attacks per month in the two months prior to the screening visit.
  - Excluded if they had difficulty distinguishing their migraine attacks from tension-type headaches; had a history of predominantly mild migraine attacks...
  - Patients with a history of cardio- vascular disorder, women who were pregnant, breastfeeding or planning to become pregnant in the next six months were excluded.
  - Due to potential pgarmacokinetic interactions with MK3207, CYP3A4 inhibitors and inducers, drugs in CYP2C family are not permitted in the study.

Method

- ii. Standard Protocol approvals, registrations, and patient consents
  - conducted in accordance with principles of Good Clinical Practice and was monitored by repre- sentatives of the study sponsor (Merck Co., Inc.).
  - approved by the ethical review commit- tee for each site and each patient provided written informed consent.
  - The trial was registered at ClinicalTrials.gov (NCT00712725).

Study Design

- Multicenter, randomized, double-blind, placebo- controlled, parallel-group study (Merck protocol 005)
- Conducted at 47 sites in the United States (19 sites), Canada (9 sites) and Europe (19 sites) between July 2008 and January 2009.
- A two-stage adaptive design, with two interim efficacy analyses, was employed to facilitate optimal dose selection.
- i. First interim efficacy analysis was performed in order to drop the less-effective dose levels from further randomization in Stage 2.
- ii.Second interim efficacy analysis was performed to test for futility and potentially add a dose group at either the low or high end of the dose range.

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.
- Double-Dummy desgin: a technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical, all patients are given both placebo and active doses in alternating periods.
- 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.
- Patients were stratified according to their self-reported retrospective usual migraine response to a triptan with a 75 percent cutline.

Stage 1

- The first interim analysis: after 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 is the lowest identified promising dose, up to 20 mg, was identified.
- "poor dose response" test: to increase the likelihood of observing 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 percent age points below the next-lower dose, all doses were to be continued into Stage 2.
- If a poor dose response was not identified, the MK-3207 dose below the lowest effective dose ("dose S-1") and higher doses were to be continued into Stage 2.

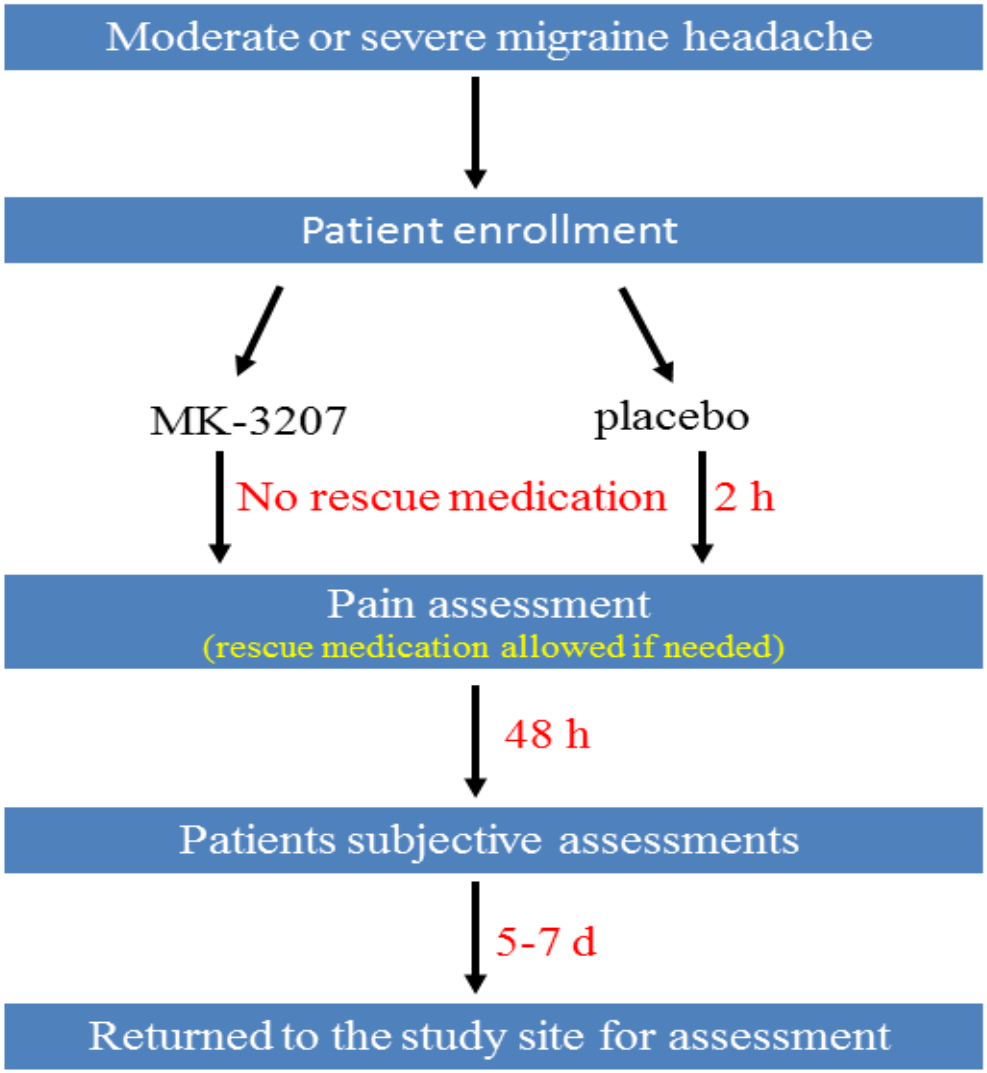
Stage 2

- 240 patients were to be ran- domly allocated to the MK-3207 dose levels remaining from Stage 1 (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 randomi- zation ratio of active MK-3207 to placebo remained at 3 : 1.

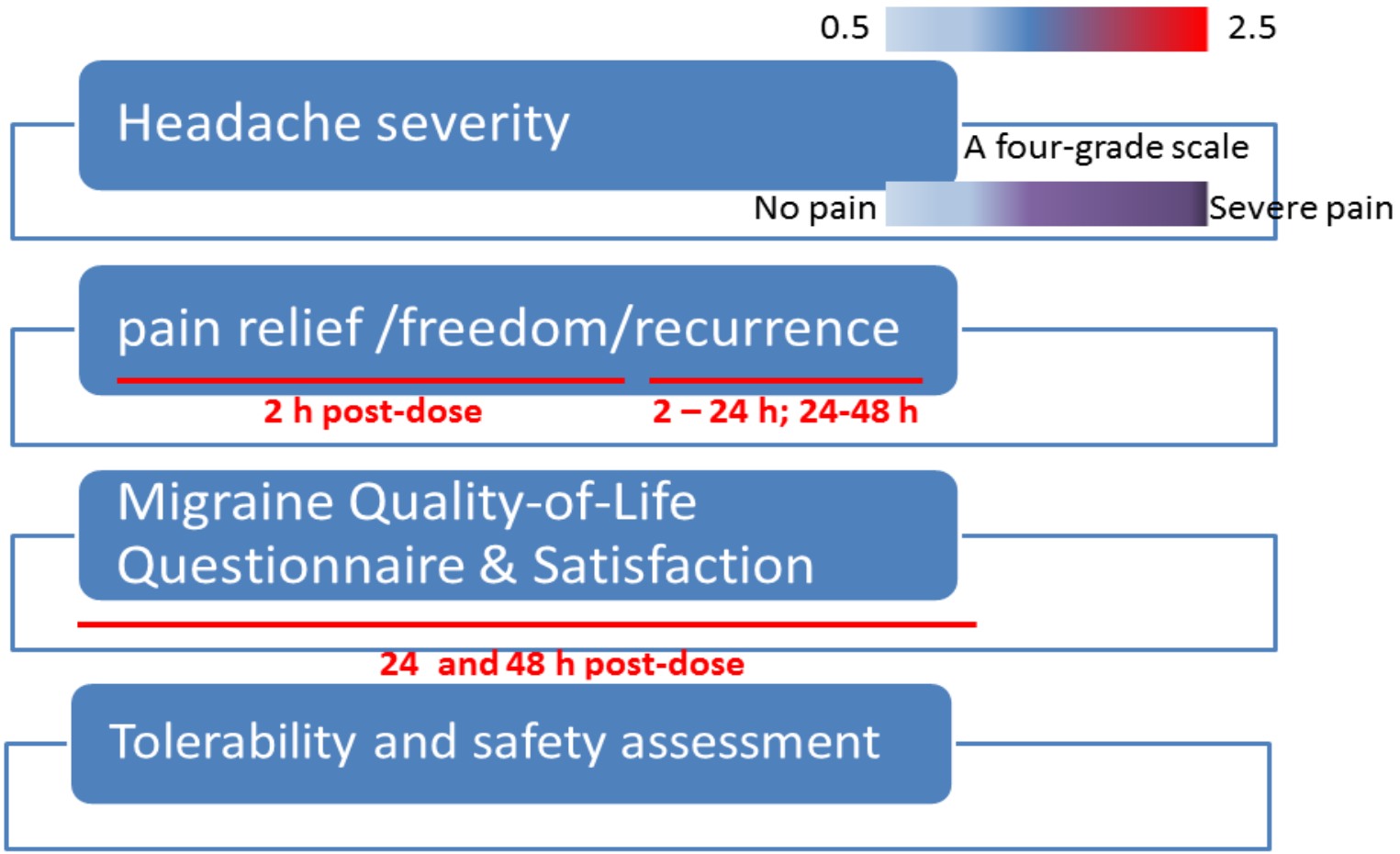
Stage 2

- The second interim analysis: 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.
- i.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).
- ii.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)

Procedures


Moderate or severe migraine headache
Patient enrollment
MK-3207
placebo
No rescue medication
2 h
Pain assessment
(rescue medication allowed if needed)
48 h
Patients subjective assessments
5-7 d
Returned to the study site for assessment

Assessments



Statistical analysis

The primary efficacy variable

The primary efficacy variable
proportion of patients reporting pain freedom at two hours post-dose.

Five secondary efficacy endpoints

(i) pain relief
(ii) absence of photophobia at two hours
(iii) absence of phonophobia at two hours
(iv) absence of nausea at two hours
(v) 2–24 hour sustained pain freedom without use of rescue medication

Statistical analysis

Hypothesis testing

1. **Question**: correlation between dosage of MK-3207 and response?
2. **Measurement**: percentage of patients achieving 2 h pain freedom.
3. **Test**: a generalized linear model.

H_o : All dose responses are the same as placebo with a response rate of 10%;
H_A: A 10% and 30% could be observed in the medicine treated groups.

Some key points

- Will at least one MK-3207 dose is superior to placebo? Yes. A pairwise comparisons of response percentages were performed using the same generalized linear regression model.
- How to perform efficacy analysis ?It was based on the Full Analysis Set (FAS) population, in which the efficacy analysis patients were counted according to the treatment group to which they were randomized.
- How to deal with the missing data?Apply the "last observation carried forward" method to impute the missing data of headache severity and associated symptoms in the FAS analysis.
- How to make sure the drug is safe to subject patients?Perform safety and tolerability assessment for all patients by review of all safety parameters, including adverse events, laboratory values, ECG and vital signs.

Patient accounting and demographics

study flow chart: values are number of patients

	Placebo	MK-3207 2.5mg	MK-3207 10mg	MK-3207 20mg	MK-3207 50mg	MK-3207 100mg	MK-3207 10mg	MK-3207 200mg
Patients randomize (676)	169	39	57	84	86	84	83	74
Patients not treated (129)	29	6	10	17	19	16	21	11
Adverse event	1	0	0	1	0	0	0	0
Patient withdrawal	2	1	1	2	1	1	1	2
Protocol violation	2	0	1	3	2	0	1	1
Lost to follow-up	3	2	1	1	2	2	2	1
Pregnancy	0	1	0	0	1	0	2	0
Physician decision	2	0	0	0	1	0	2	0
Lack of qualifying migraine	16	2	6	8	11	13	11	6
Other protocol specified criteria	3	0	1	2	1	0	2	1
Patients treated (547)	140	33	47	67	67	68	62	63
Completed	140	33	47	67	67	68	61	63
Discontinued	0	0	0	0	0	0	1	0
Patients analyzed for efficacy (517)	133	32	44	63	63	65	59	58
Patients not analyzed for efficacy	7	1	3	4	4	3	3	5
No baseline data	1	0	0	0	0	0	1	0
No post-dose data up to 2 hours	1	1	1	0	0	2	1	0
Questionable data from one site	5	0	2	4	4	1	2	5
Patients analyzed for safety	142	32	47	66	67	68	62	63

- CONSORT = Consolidated Standards of Reporting Trials. Placebo is the pooled arm of all matching placebo doses.
-Patients may have been excluded for more than one reason.
- Includes two patients from the active treatment groups who actually took placebo, due to taking treatment from only one of the two study medication bottles that they were provided with (one contained active treatment and one contained placebo).
- One patient actually took placebo, due to taking treatment from only one of the two study medication bottles that they were provided with (one contained active treatment and one contained placebo), so their data is counted in the placebo group for the safety analysis.

Patient accounting and demographics

Table 2. Patient demographics and characteristics of treated migraine attacks at baseline: values are number (%) of patients except for age, where the mean (SD) is given

	Placebo (N = 140)	MK-3207 2.5 mg (N = 33)	MK-3207 5 mg (N = 47)	MK-3207 10 mg (N = 67)	MK-3207 20 mg (N = 67)	MK-3207 50 mg (N = 68)	MK-3207 100 mg (N = 62)	MK-3207 200 mg (N = 63)
Patient characteristics								
Female	125 (89.3)	27 (81.8)	40 (85.1)	62 (92.5)	54 (80.6)	62 (91.2)	52 (83.9)	54 (85.7)
Mean (SD) age, years	42.1 (11.2)	43.3 (10.5)	43.4 (11.1)	44.1 (10.0)	44.1 (11.3)	42.2 (10.8)	42.4 (10.9)	40.5 (10.7)
White	132 (94.3)	32 (97.0)	46 (97.9)	62 (92.5)	63 (94.0)	64 (94.1)	59 (95.2)	59 (93.7)
US	66 (47.1)	14 (42.4)	22 (46.8)	30 (44.8)	39 (58.2)	45 (66.2)	34 (54.8)	20 (31.7)
Using prophylaxis	37 (26.4)	11 (33.3)	14 (29.8)	21 (31.3)	19 (28.4)	17 (25.0)	18 (29.0)	20 (31.7)
Ever treated migraine with triptan	117 (83.6)	28 (84.8)	39 (83.0)	53 (79.1)	56 (83.6)	47 (69.1)	49 (79.0)	54 (85.7)
Usual treatment includes a triptan	96 (68.6)	21 (63.6)	30 (63.8)	42 (62.3)	42 (62.3)	41 (60.3)	38 (61.3)	44 (69.8)
75–100% of headaches respond to triptans	77 (55.0)	18 (54.5)	24 (51.1)	37 (55.2)	37 (55.2)	33 (48.5)	31 (50.0)	35 (55.6)
Baseline characteristics of treated attack*								
Moderate headache	95 (67.9)	25 (75.8)	36 (76.6)	45 (67.2)	43 (64.2)	47 (69.1)	43 (69.4)	38 (60.3)
Severe headache	43 (30.7)	8 (24.2)	11 (23.4)	22 (32.8)	24 (35.8)	21 (30.9)	18 (29.0)	25 (39.7)
With aura	30 (21.4)	7 (21.2)	15 (31.9)	13 (19.4)	8 (11.9)	15 (22.1)	8 (12.9)	17 (27.0)
With photophobia	110 (78.6)	31 (93.9)	40 (85.1)	55 (82.1)	56 (83.6)	56 (82.4)	54 (87.1)	51 (81.0)
With phonophobia	108 (77.1)	27 (81.8)	37 (78.7)	46 (68.7)	57 (85.1)	51 (75.0)	46 (74.2)	48 (76.2)
With nausea	76 (54.3)	21 (63.6)	33 (70.2)	38 (56.7)	35 (52.2)	40 (58.8)	30 (48.4)	29 (46.0)
With vomiting	3 (2.1)	2 (6.1)	1 (2.1)	5 (7.5)	9 (13.4)	1 (1.5)	1 (1.6)	3 (4.8)
With functional impairment	130 (92.9)	33 (100.0)	45 (95.7)	63 (94.0)	65 (97.0)	66 (97.1)	61 (98.3)	60 (95.2)

SD = standard deviation.
*Baseline = 0 hours, immediately before patient took study drug.

Dose Selection Across 3 Stages

	Dose (mg)							
Stage 1	0	2.5	5	10	20	50	100	
	lowest effective dose S: over 15% S = 10mg remain S – 1 and above							
Stage 2	0		5	10	20	50	100	
	added 200-mg dose treatment gain over placebo in 20mg, 50mg, and 100mg are all ≤ 15%							
Stage 3	0		5	10	20	50	100	200

- No poor dose response was observed after Stage 1.
- The adaptive strategy resulted in final sample sizes for the 2.5 and 5mg groups that were smaller than for the other MK-3207 dose groups.

Effecacy

Table 3. Summary of efficacy of treatment on primary and secondary endpoints

	Statistics	Placebo (*N* = 133)	MK-3207 2.5 mg (*N* = 32)	MK-3207 5 mg (*N* = 44)	MK-3207 10 mg (*N* = 63)	MK-3207 20 mg (*N* = 63)	MK-3207 50 mg (*N* = 65)	MK-3207 100 mg (*N* = 59)	MK-3207 200 mg (*N* = 58)	Trend test† *p* value
Primary endpoint										
Pain freedom at 2 hours	n	13	4	5	16	12	14	14	21	<0.001
	Observed %	9.8	12.5	11.4	25.4 *	19.0	21.5	23.7 *	36.2 ***	
	(95% CI)	(5.3, 16.1)	(3.5, 29.0)	(3.8, 24.6)	(15.3, 37.9)	(10.2, 30.9)	(12.3, 33.5)	(13.6, 36.6)	(24.0, 49.9)	
Secondary endpoints										
Pain relief at 2 hours	n	48	15	19	36	36	41	31	40	<.001
	Observed %	36.1	46.9	43.2	57.1 **	57.1 **	63.1 ***	52.5 *	69.0 ***	
	(95% CI)	(27.9, 44.9)	(29.1, 65.3)	(28.3, 59.0)	(44.0, 69.5)	(44.0, 69.5)	(50.2, 74.7)	(39.1, 65.7)	(55.5, 80.5)	
No photophobia at 2 hours	n	51	10	15	32	27	32	26	33	.005
	Observed %	38.3	31.3	34.1	50.8	42.9	49.2	44.1	56.9*	
	(95% CI)	(30.1, 47.2)	(16.1, 50.0)	(20.5, 49.9)	(37.9, 63.6)	(30.5, 56.0)	(36.6, 61.9)	(31.2, 57.6)	(43.2, 69.8)	
No phonophobia at 2 hours	n	57	12	18	35	35	38	31	37	<.001
	Observed %	42.9	37.5	40.9	55.6	55.6	58.5 *	52.5	63.8 **	
	(95% CI)	(34.3, 51.7)	(21.1, 56.3)	(26.3, 56.8)	(42.5, 68.1)	(42.5, 68.1)	(45.6, 70.6)	(39.1, 65.7)	(50.1, 76.0)	
No nausea at 2 hours	n	79	19	2	44	42	44	41	45	.007
	Observed %	59.4	59.4	58.1	69.8	66.7	67.7	69.5	77.6 **	
	(95% CI)	(50.5, 67.8)	(40.6, 76.3)	(42.1, 73.0)	(57.0, 80.8)	(53.7, 78.0)	(54.9, 78.8)	(56.1, 80.8)	(64.7, 87.5)	
2–24 hour sustained pain freedom	n	10	4	2	13	10	12	12	17	<.001
	Observed %	7.5	12.5	4.5	20.6	15.9	18.5	20.3	30.4 **	
	(95% CI)	(3.7, 13.4)	(3.5, 29.0)	(0.6, 15.5)	(11.5, 32.7)	(7.9, 27.3)	(9.9, 30.0)	(11.0, 32.8)	(18.8, 44.1)	
Exploratory endpoint										
2-48 hour sustained pain freedom	n	7	3	2	10	7	10	11	16	<0.001
	Observed %	5.3	9.4	4.5	16.1*	11.5	15.4	18.6*	28.6*	
	(95% CI)	(2.1, 10.5)	(2.0, 25.0)	(0.6, 15.5)	(8.0, 27.7)	(4.7, 22.2)	(7.6, 26.5)	(9.7, 30.9)	(17.3, 42.2)	

N = number of patients in endpoint-specific full analysis set (FAS) population for primary endpoint; numbers were similar for other endpoints. n = number of treatment responders for the specific endpoint. CI = confidence interval. Placebo is the pooled arm of all matching placebo doses. *$p \leq 0.050$, **$p \leq 0.010$, ***$p \leq 0.001$ for MK-3207 vs. placebo pairwise comparison based on the model adjusting for baseline headache severity, geographic region, age and usual triptan response.
†Trend test is based on generalized linear regression model adjusting for geographic region, baseline severity, usual triptan response and age with continuous covariate for treatment.

Tolerability and Safety

Table 4. Number (%) of patients reporting clinical adverse events within 14 days post-dose

	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.

1. Construct a set of candidate model : Fitting several different models
2. Choose the best model
3. Obtaining Target dose and Effective dose

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

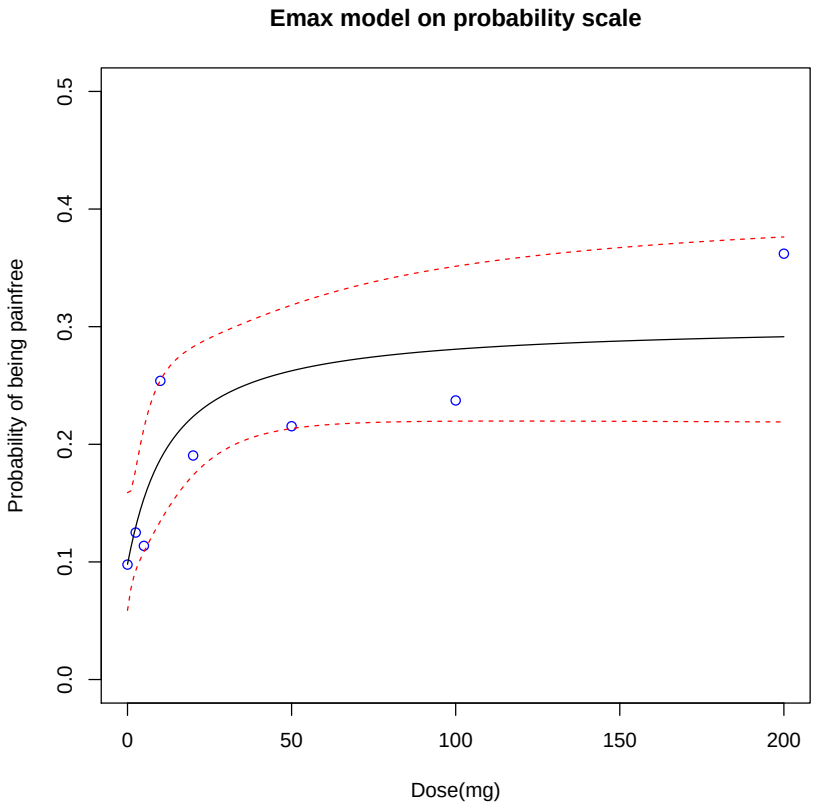
- This model is intended to capture a possible non-monotonic dose-response relationship.
- β_2 parameter controls whether model is convex or concave.

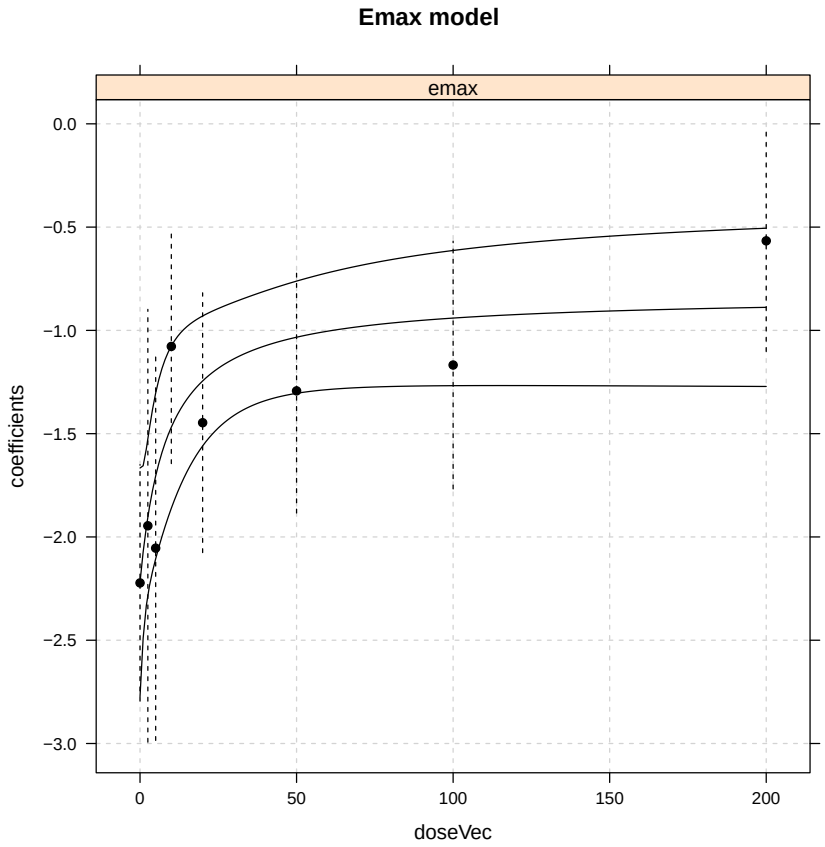
Logistic $= f(d, \theta) = E_0 + E_{max}/\{1 + exp[(ED_{50} - d)/\delta]\}$

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

Construct a set of candidate models

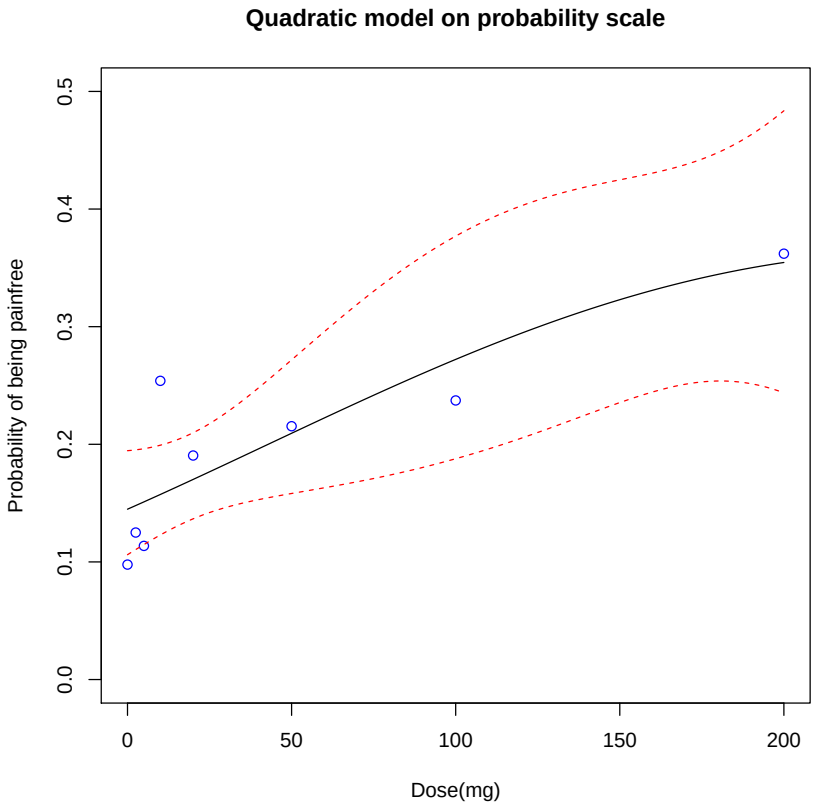
Emax model

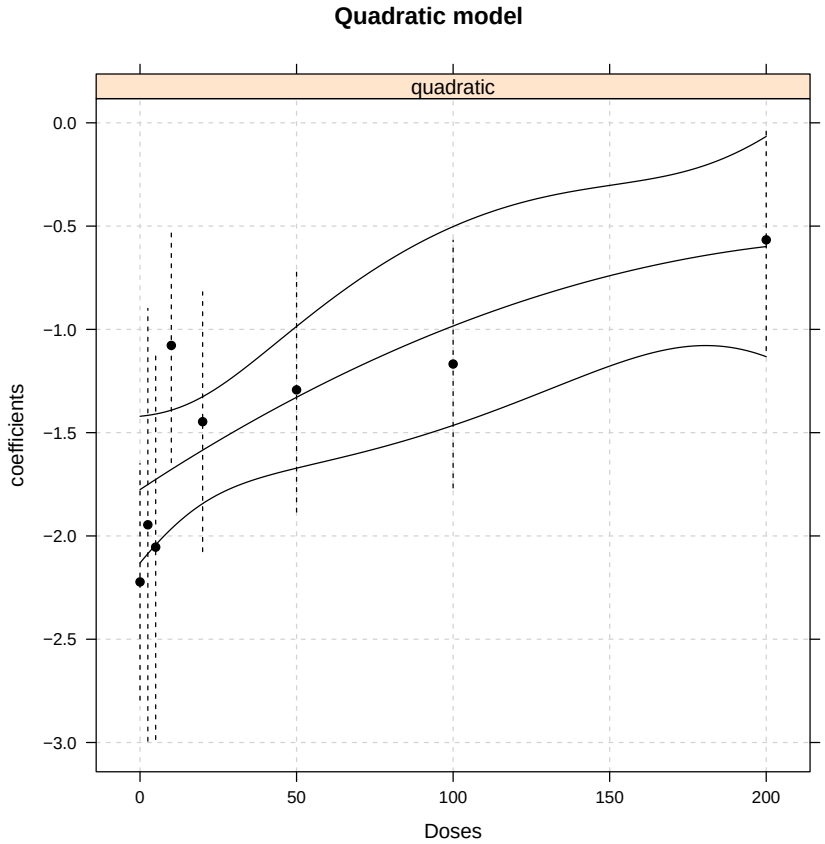




Construct a set of candidate models

Quadratic model





MCP-Mod

Choose the best model

1. AIC: Selects model with smallest AIC (this is the default)
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: $w_i = exp(-0.5AIC_i)/\sum_i(exp(-0.5AIC_i))$

MCP-Mod

Choose the best model

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

- Based on maxT, Quadratic model is the best.
- Based on AIC/aveAIC, Emax model is the best.

Target doses

- The TD(target dose) is defined as the dose that achieves a target effect of Δ over placebo

$$TD_{\Delta} = min\{x|f(x) > f(0) + \Delta\}$$

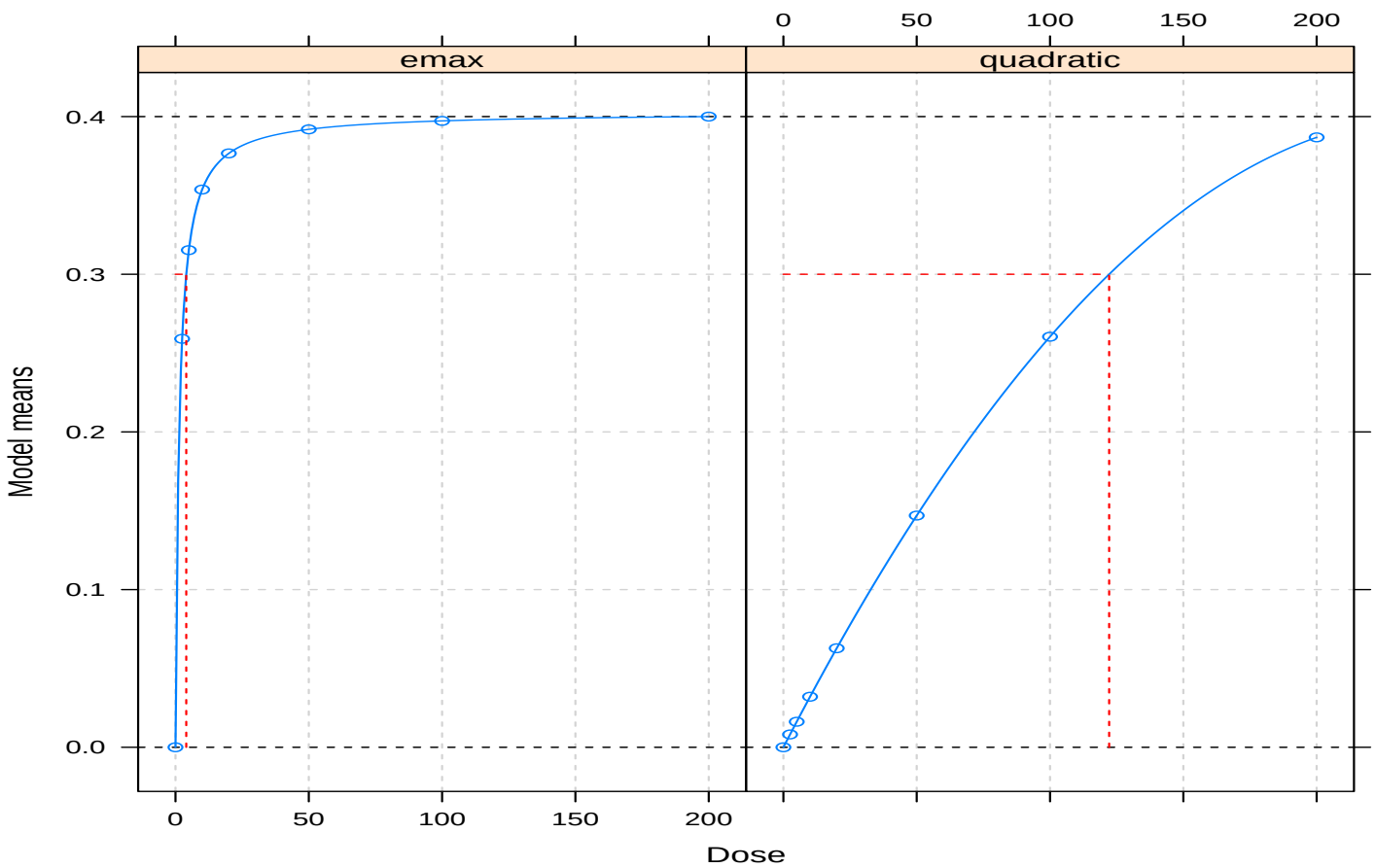
- When Δ is the clinical relevance threshold, then TD is similar to the usual definition of the minimum effective dose(MED).

TD table

	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	

- TDs from the four candidate models are averaged with weights using **aveAIC**.

TD plot



Effective dose

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.

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

ED table

	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