

Lasmiditan (COL-144) a Selective 5-HT_{1F} Agonist, is a Rapid & Effective Oral Treatment for Acute Migraine

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BACKGROUND

Migraine is a common and disabling disorder and the need for an effective and rapid treatment for the acute attack is only partly satisfied by the triptans. Typically only 50-60% of attacks respond to an oral triptan within 2 hours and even then symptoms may recur within 24 hours. Because of their potential to constrict coronary and cerebral vessels triptans are contraindicated in patients with vascular disease and although ischemic adverse events are rare, the more common chest, neck, and jaw heaviness or pressure may be poorly tolerated and cause diagnostic confusion.

Lasmiditan (COL-144) is a novel molecule with a neural mechanism of action and, unlike triptans, it exhibits anti-migraine activity without causing vasoconstriction. It is a highly potent and selective 5-HT_{1F} receptor agonist (Ki at human 5-HT_{1F} receptors of 2.2 nM), possessing >450-fold higher affinity for the 5-HT_{1F} receptor versus 5-HT_{1B} or 1D receptors based on binding affinity in vitro¹.

Drug	5-HT _{1A}	5-HT _{1B}	5-HT _{1D}	5-HT _{1E}	5-HT _{1F}
Sumatriptan	>10,000	70	2.6	>10,000	250
Zolmitriptan	>10,000	18	0.8	62	420
Rosazatriptan	>10,000	120	4.5	870	2500
Frovatriptan	1,150	20	2.3	>10,000	370
COL-144	>10,000	>10,000	>1,000	>10,000	43

When given intravenously, lasmiditan proved effective in the acute treatment of migraine². A tablet formulation of lasmiditan has been developed which shows rapid absorption, linear pharmacokinetics and an oral bioavailability of about 40%.

STUDY DESIGN

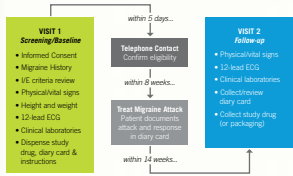
- Prospective, randomized, double-blind, placebo-controlled parallel-group study
- Patients randomised to oral lasmiditan (50, 100, 200 or 400mg) or matching placebo in a 1:1:1:1:1 ratio.
- All patients received 2 small (50mg or placebo) and 2 medium (200mg or placebo) tablets

PATIENT SELECTION

Patients were selected for the study who met the IHS diagnostic criteria 1.1 and 1.2.1 (2004)³, experienced 1-8 attacks a month and were not taking prophylaxis medication.

STUDY PROCEDURES

The study was conducted in accordance with the Declaration of Helsinki and internationally accepted standards of Good Clinical Practice. Prior to initiation it was approved by the relevant regulatory authorities and independent ethics committees. All subjects gave written informed consent.



OBJECTIVES OF THE STUDY

Primary: evaluate the efficacy based on headache response (moderate or severe headache becoming mild or none at two hours) of a range of oral doses of lasmiditan in order to select a dose or doses for further evaluation.

Secondary: explore the time course and effect of lasmiditan on features of the migraine including: headache response, proportion of patients pain-free, headache recurrence, nausea, photophobia, phonophobia, vomiting, disability, use of rescue medication and patient global impression.

Safety: explore the safety and tolerability of lasmiditan in terms of adverse events, physical exam, vital signs, laboratory evaluations, and ECGs.

STATISTICAL METHODS AND SAMPLE SIZE

The primary efficacy analysis was a modified intent to treat analysis testing the null hypothesis that the proportions of patients with headache relief 2 hours post dose are the same in the five study arms, versus the alternative hypothesis of a positive linear trend in the response rates, using the Cochran-Armitage test for trend⁴. For the primary efficacy parameter, if the test for trend was significant then hierarchical pair wise testing of individual dose groups versus placebo was conducted.

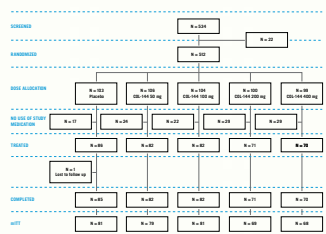
Sample size was estimated assuming a response rate of 40% in the placebo arm and a 65% rate in the highest active dose arm using the approach of Nam⁵. Based on 1:1:1:1:1 randomization, a total sample size of 330 evaluable patients (66 per group) was required for 90% power and a two-sided test at the 5% level of significance.

PATIENT POPULATION

534 patients were screened and randomised. Of these 391 treated an attack with study medication and were evaluated for safety. 378 patients qualified for the primary modified intent-to-treat (mITT) analysis. Patients were only excluded from the mITT analysis if they did not take all study medication, used other medication first for this attack, did not treat a moderate/severe attack or failed to record baseline headache severity.

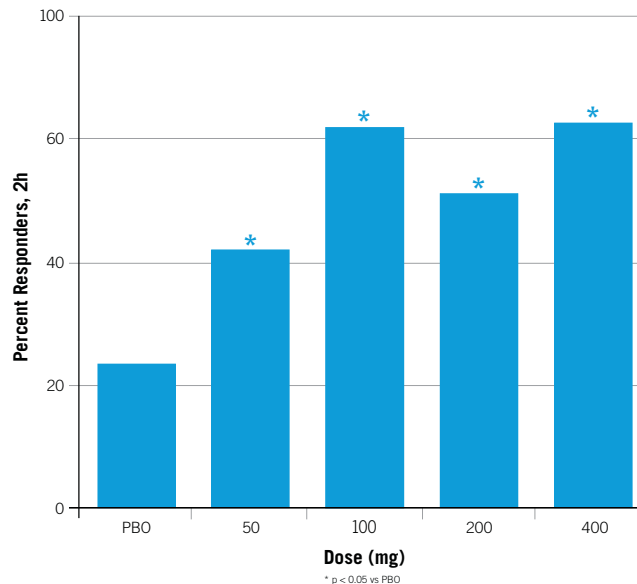
As is typical of this type of study, most (87.5%) of the patients were female and the mean age was 40 years. The groups were well balanced except that patients in the 200mg group reported more severe headaches at baseline (48.6% vs. 42% overall). Median time to treatment was 1.8 – 2.8h after the start of the attack and 0.2 h after the attack became moderate/severe.

Patient Disposition

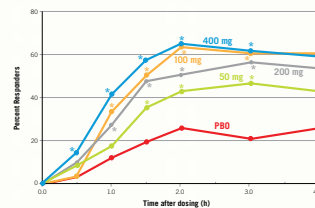


RESULTS – EFFICACY

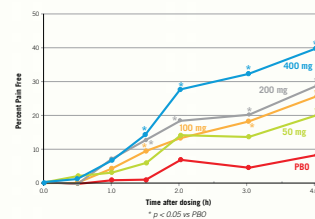
Headache Response at 2h. Reduction of a moderate or severe headache at baseline to mild or none 2 hours after dosing.



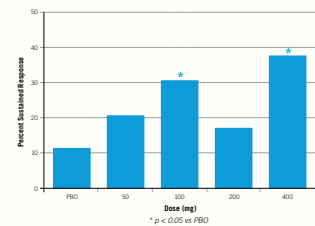
Headache Response Over Time



Pain Free Over Time



Sustained Response. Moderate or severe headache at baseline that becomes mild or none at 2h and does not recur (become moderate or severe) within 24 hours



Associated Migraine Symptoms

Both photophobia and phonophobia showed a significant dose related reduction at or before 2 h after treatment. For nausea this became statistically significant from 3 h.

RESULTS – SAFETY

Adverse Events

Treatment-emergent adverse events were reported by 22% of the patients receiving placebo and by 65, 73, 86 and 84% of patients receiving 50, 100, 200 and 400mg lasmiditan, respectively. The most common adverse events seen in the lasmiditan groups related to the nervous system. Most reported events of heaviness were localized to the limbs. Chest symptoms characteristic of triptan use were rare, occurring with a similar frequency in the placebo and active groups. Adverse events with a total incidence of >5% of patients in the study are as follows:

Adverse Event	Dose of COL-144 (mg)				
	PBO	50	100	200	400
Dizziness	1.2	23.2	28.0	38.0	37.1
Fatigue	2.3	12.2	20.7	21.1	24.3
Vertigo	1.2	9.8	14.6	16.9	24.3
Somnolence	2.3	9.8	12.2	11.3	11.4
Paresthesia	2.3	2.4	11.0	16.9	20.0
Heaviness	1.2	4.9	4.9	9.9	7.1
Nausea	0.0	4.9	11.0	4.2	7.1

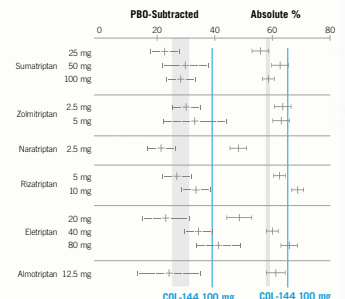
One serious adverse event occurred in the study – moderate dizziness in a female patient receiving 200mg lasmiditan. The patient recovered without sequelae.

There were no clinically significant changes in laboratory parameters, ECGs or vital signs.

CONCLUSIONS

Lasmiditan, a selective and specific agonist at the 5-HT_{1F} receptor, is an effective acute treatment for migraine when given orally. It showed a significant dose response relationship for headache response rate and headache pain free with onset of headache relief as early as 30 min in the highest dose group. Lasmiditan is effective not only against the headache but also against other migraine symptoms such as phonophobia, photophobia and nausea.

Placebo responses may range from 25 to greater than 50% in acute migraine studies. In this study the placebo response rate was relatively low compared to other acute migraine studies published recently. This may reflect the care taken at the study sites to ensure that only patients with a clear diagnosis of migraine participated in the study and also the severity of the disease in the population treated at these specialist centres. In making comparisons with historical data from triptan studies it is therefore important to consider both the absolute response rate and the placebo-subtracted response. When compared with a large triptan meta-analysis⁶ the 100mg dose of lasmiditan is at least as, if not more, effective in relieving headache at 2h.



Ferrari et al (2002) Cephalgia 22, 643

Lasmiditan is believed to act via a neural mechanism and this is consistent with the adverse event profile suggesting penetration of the drug into the central nervous system. Unlike triptans, lasmiditan lacks vasoconstrictor activity¹.

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Participating Investigators
 We would like to acknowledge the contribution of the following investigators and to thank the patients who took part in the study.
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Prediction of therapeutically effective dose of COL-144 based on relationship between plasma concentrations and headache response

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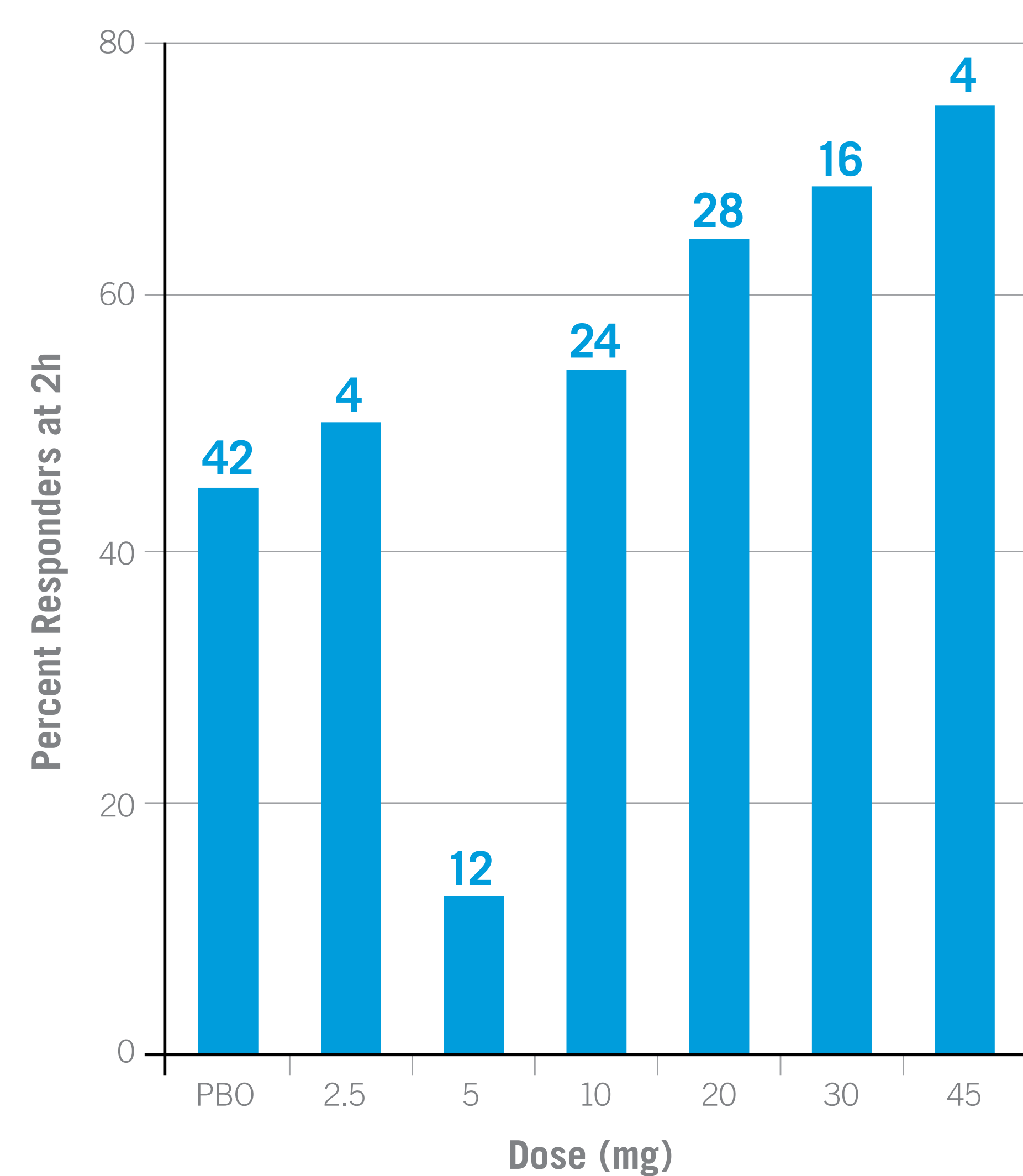
OBJECTIVE

To predict an oral dose range of COL-144 that is at least as effective as sumatriptan in the acute treatment of migraine.

BACKGROUND

- COL-144, a Neurally Acting Anti-Migraine Agent (NAAMA), is a selective agonist at 5-HT_{1F} receptors that, unlike triptans, is not a vasoconstrictor¹.
- In a Phase II trial with an adaptive dose allocation design, the efficacy of COL-144 given as an i.v. infusion was established (Figure 1)².
- The relationship between plasma concentration and headache response was analyzed using population pharmacokinetic-pharmacodynamic (PK-PD) modeling.
- A subsequent Phase I trial studied the PK of an oral liquid formulation of COL-144 (see Pilgrim et al poster, this meeting). Using the relationship between plasma levels and headache response, together with the oral PK of COL-144, an oral dose range was predicted that is expected to provide acute migraine relief.

Figure 1: Proportion of patients with headache response 2 hours post dose
Bars represent proportion of responders per dose group; numbers above bars represent number of subjects included per dose group.



METHODS

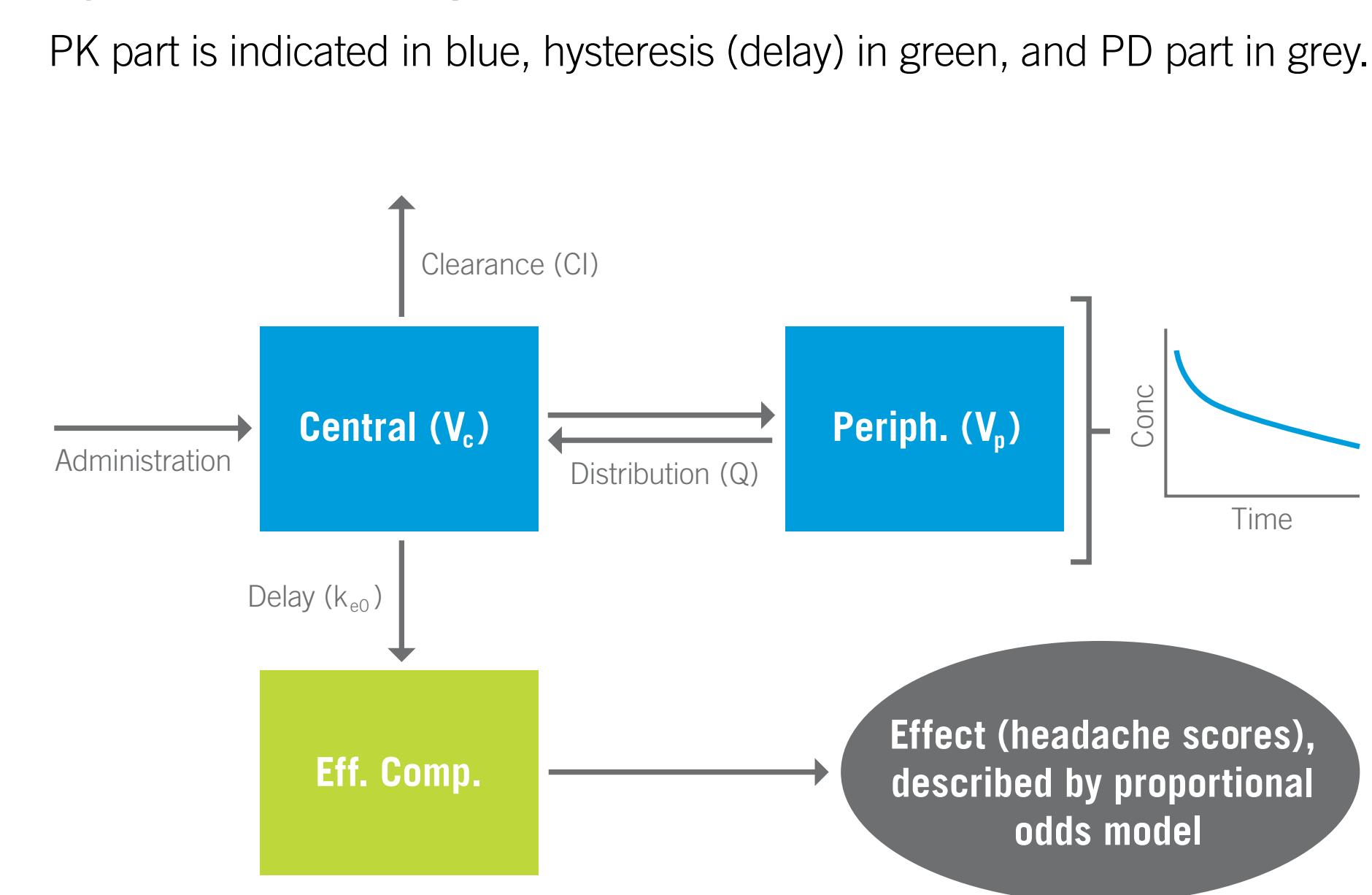
Data available

- Phase II trial (intravenous infusion of COL-144 over 20 min):
 - Doses: Placebo (n=42), 2.5 mg (n=4), 5 mg (n=12), 10 mg (n=24), 20 mg (n=28), 30 mg (n=16), 45 mg (n=4)
 - PK measured and headache scored (4 point scale; 0-3 no headache to severe headache) for 4 hours
- Phase I trial (oral liquid formulation of COL-144):
 - Doses: 25 mg (n=6), 50 mg (n=6), 100 mg (n=14), 200 mg (n=6), 300 mg (n=6) and 400 mg (n=14)
 - PK measured for 30 hours

Background PK-PD modeling

- Plasma concentration versus time profiles are described by compartmental models (Figure 2, upper part): drug is assumed to distribute into one or more interconnected hypothetical compartments, which mimics drug absorption, distribution, and elimination processes.

Figure 2: Schematic representation of PK-PD model



- Target site is often in organ or peripheral tissue, rather than in plasma. Therefore, distribution to target site may cause delay (hysteresis). In general, this is accounted for using an "effect compartment model":

$$\frac{dC_e}{dt} = k_{e0} \times (C_p - C_e)$$

- C_e : concentration at effect site; C_p : plasma concentration; k_{e0} : rate constant to describe delay
- The resulting continuous description of the concentration at the target site is linked to the observed effect using a PD model. Many PD models have been developed with varying complexity based on physiological and mechanistic assumptions.

Modeling steps

- A population PK-PD model was developed to describe the relationship between plasma concentration and headache response:
 - Headache response was a categorical response (scores 0/1/2/3 i.e., none/mild/moderate/severe), which was modelled using a proportional odds model:
 - "Estimation of time course of probability to have a given score after administration of placebo (natural time course of attack) or drug (drug effect on headache)".
 - Example:

$$P_0 = P_0 \text{ at time } = 0 + f(C(\text{time})) + \text{plac}(\text{time})$$

P_0 : Probability to have score 0 at time = 0
 $f(C(\text{time}))$: Dependent on concentration, which is described as function of time (PK analysis)
 $\text{plac}(\text{time})$: Dependent on time: natural decline & placebo effect

- A population PK model was developed to describe the concentration-time profile of COL-144 in plasma after oral administration.
 - Hysteresis (delay) between plasma concentration and effect on headache response is described using "effect compartment model".
- A population PK model was developed to describe the concentration-time profile of COL-144 in plasma after oral administration.

- Using the PK model for oral COL-144, combined with the concentration-effect relationship, the minimal effective oral dose of COL-144 was predicted as follows:

- Dose should give a faster onset of headache response and/or higher response rate than intranasal sumatriptan (20 mg):
 - Pain Relief (score 3/2 to 1/0; placebo corrected) should be at least 12% after 30 min.
 - Placebo corrected Pain Relief was used, because headache response in placebo treated subjects differs between trials.

Data analysis was performed using NONMEM® version 6.2.

RESULTS

The resulting PK-PD model adequately described the headache scores after all intravenous doses of COL-144 (Figure 3).

Figure 3: Cumulative probability to have a certain headache score versus time
Dots represent observed headache response; lines represent predictions by PK-PD model; shaded areas indicate prediction uncertainty, obtained from the uncertainty of the parameter estimates. Doses were administered intravenously.

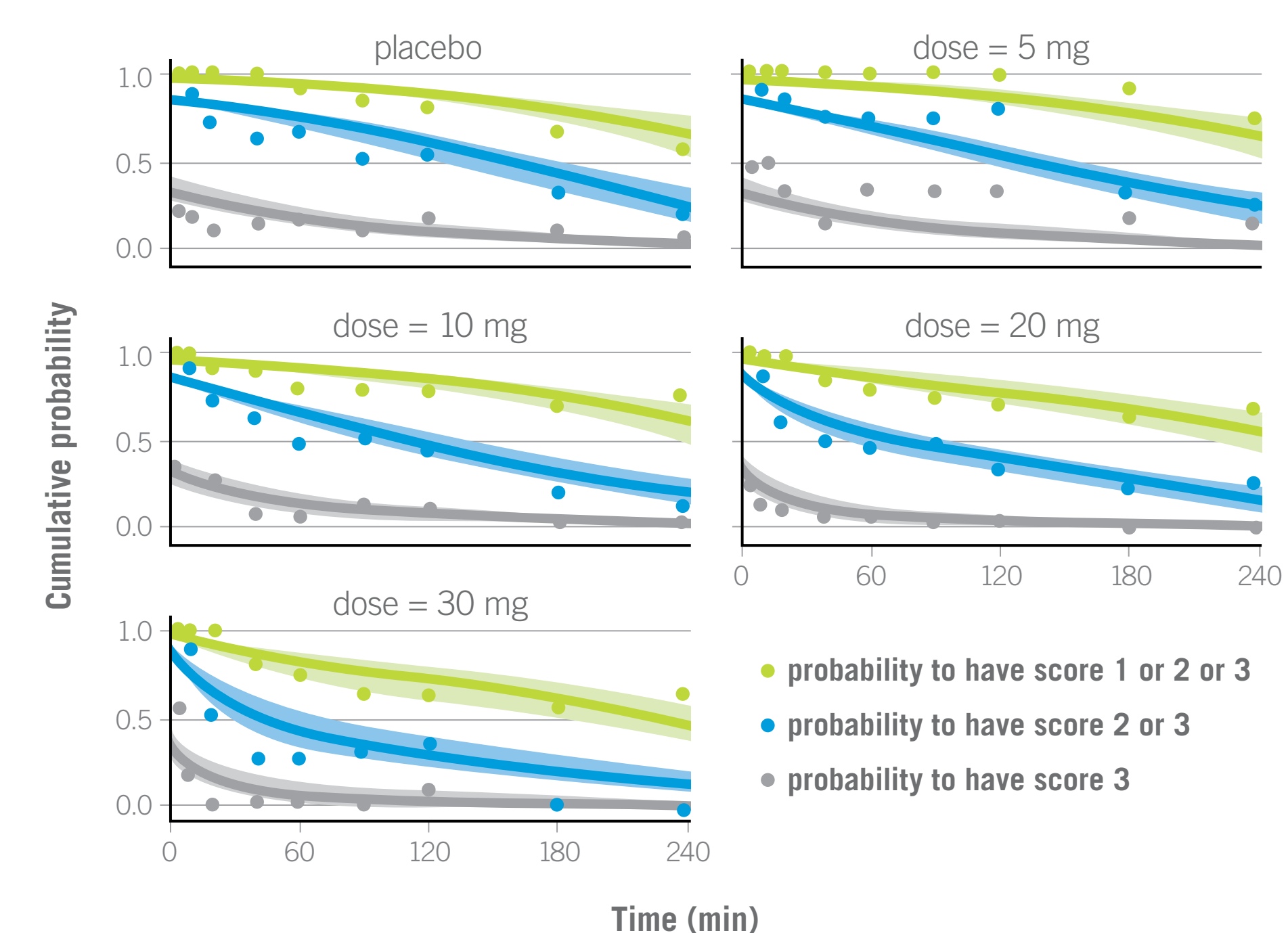


Figure 4: Examples of concentration time profiles after different oral doses
Dots represent measured plasma concentrations; lines represent individual predictions by PK model; broken lines represent population predictions by PK model (prediction for typical subject in population). Doses were administered orally.

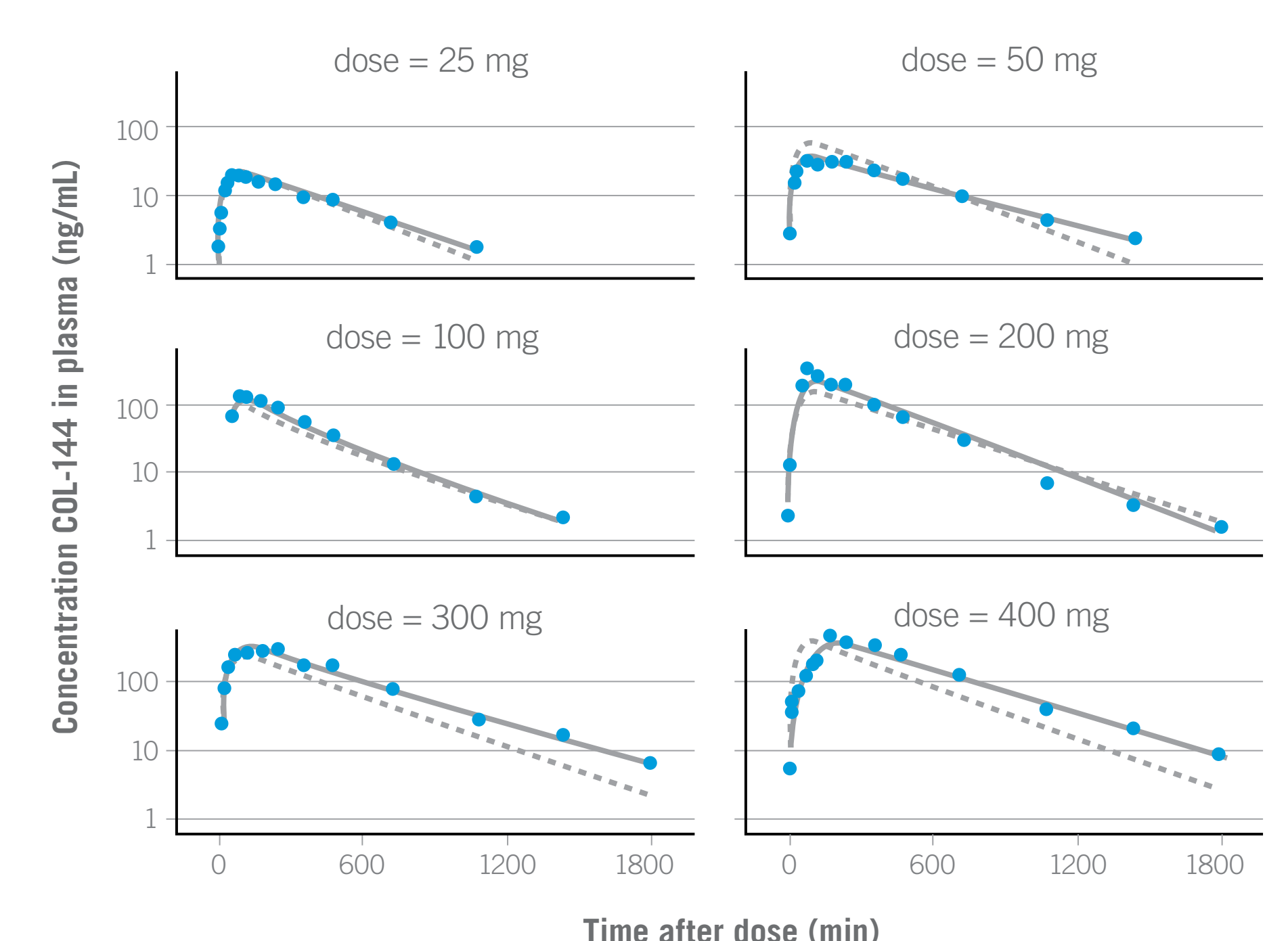
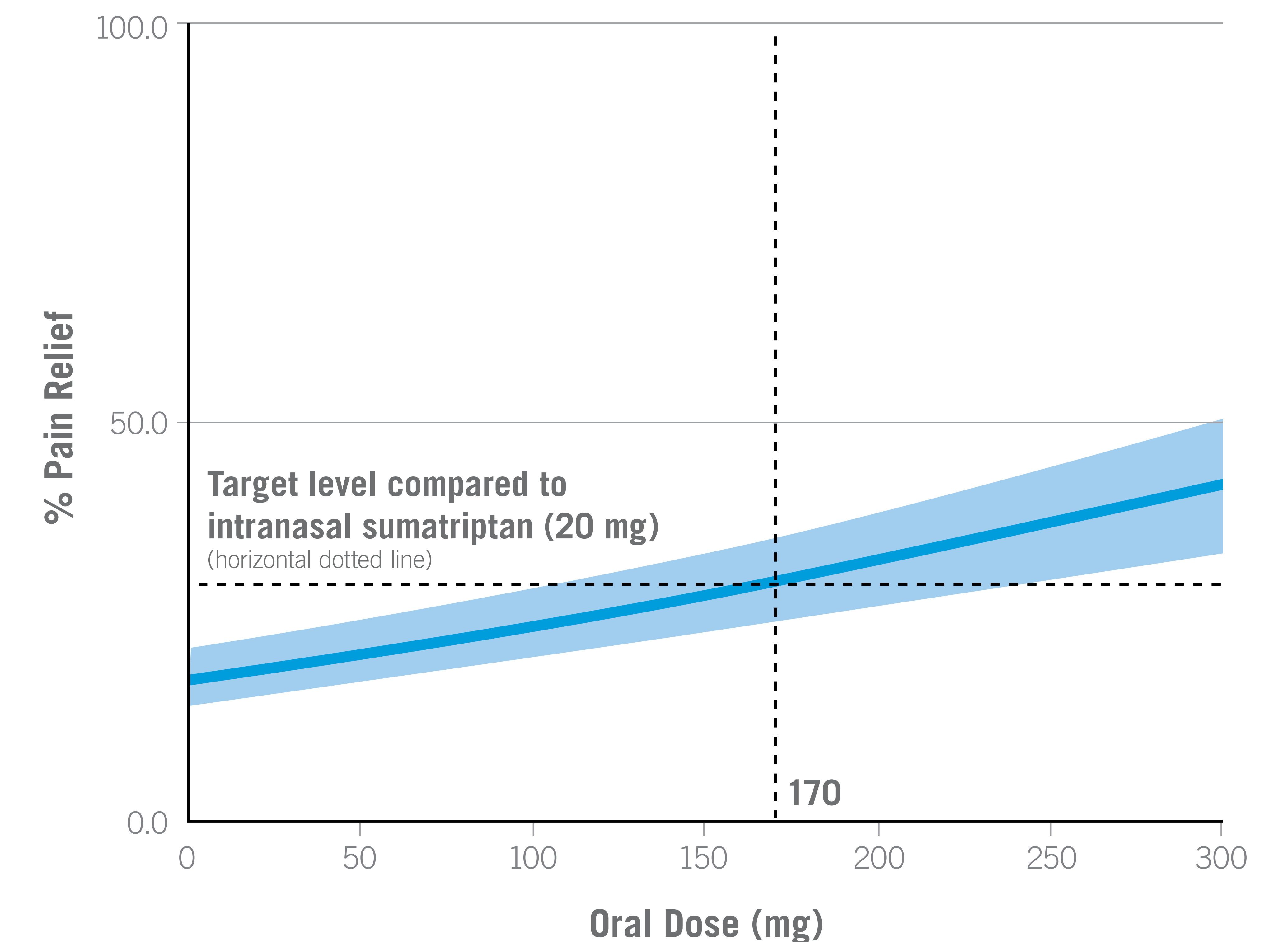


Figure 5: Percent Pain Relief at 30 min post dose versus time to select an effective oral dose

Line represents median prediction of percent pain relief by PK-PD model; shaded areas indicate prediction uncertainty, obtained from the uncertainty of the parameter estimates.

Target level compared to intranasal sumatriptan: placebo corrected pain relief should be at least 12%. Since the placebo response in the Phase II trial was 18%, pain relief should be at least 30%.



RESULTS (CONTINUED)

The PK model adequately described the concentration-time profiles after oral administration of different doses of COL-144 (Figure 4).

The model was used to predict migraine relief at 30 minutes after oral dosing of COL-144 (Figure 5).

- The target level derived from published sumatriptan data is indicated in Figure 5.
- The predicted oral dose range needed to reach the desired therapeutic target is 170 mg and above.

CONCLUSIONS

- A PK-PD model was developed, which adequately described the relation between plasma concentration and response (headache scores).
- On the basis of this concentration versus response relationship, a likely effective dose range for an oral dose ranging study in migraine using an oral tablet formulation was identified.

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Financial Support

This work was sponsored by Colucid Pharmaceuticals, Inc.

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