1 Synopsis

Title of the study

A double-blind randomized placebo-controlled parallel group dose-ranging study of oral COL-144 in the acute treatment of migraine

Investigators and study centers

A total of 43 centers and investigators: 5 centers in Belgium, 7 centers in Finland, 6 centers in France, 16 centers in Germany and 9 centers in Spain.

Coordinating investigators

PPD, Liege, Belgium; PPD Helsinki, Finland; PPD, France; PPD, Essen, Germany and PPD, Valencia, Spain

Publication (reference): not applicable

Study period: 08-Jul-2009 (first patient in) to 18-Feb-2010 (last patient out)

Clinical phase: 2

Objectives

Primary efficacy objective

To evaluate the efficacy (headache response at 2 hours) of a range of oral doses of COL-144 in order to select a dose or doses for further evaluation.

Secondary efficacy objective

To explore the time course and effect of a range of doses of COL-144 on features of migraine including: headache response, proportion of patients pain-free, headache recurrence, nausea, photophobia, phonophobia, vomiting, clinical disability, use of rescue medication and patient global impression.

Safety objective

To explore the safety and tolerability of a range of doses of COL-144 in terms of adverse events (AEs), physical examination, vital signs, laboratory evaluations and electrocardiograms (ECGs).

Methodology

This was a prospective, randomized, double-blind, placebo-controlled, dose-ranging study in patients with migraine. Patients were asked to treat a single migraine attack with study medication at home. Each patient's study participation consisted of a screening visit with a telephone contact within 5 days* to confirm eligibility, a treatment period of up to 8 weeks

* In France and Spain, the telephone contact was replaced by an additional visit when eligibility was confirmed prior to dispensing the study medication and diary card (see country-specific amendments in Section 9.8).

during which the patient was asked to treat one acute migraine attack with a single dose of COL-144 (50, 100, 200 or 400 mg) or placebo, and a follow-up visit within 14 days of treating an attack. Following screening, patients were randomly assigned to receive oral COL-144 (50, 100, 200 or 400 mg) or matching placebo (1:1:1:1:1). Eligible patients were asked to treat their next migraine attack within 4 hours of its onset providing that the headache severity was at least moderate at that time and not improving. Patients recorded their response over the next 48 hours using a diary card. Patients were instructed not to use rescue medication until at least 2 hours after taking the study medication. Once an attack had been treated, patients contacted the clinic to schedule a follow-up visit as soon as possible and no more than 14 days after treatment.

Number of patients (total and for each treatment group) planned and analyzed

Planned: at least 330 evaluable patients (66 patients in each treatment group)

Analyzed:

	Enrolled and randomized (N)	ITT (=SAF) (N)	mITT[a] (N)	PP (N)
Placebo	103	86	81	67
50 mg COL-144	106	82	79	67
100 mg COL-144	104	82	81	58
200 mg COL-144	100	71	69	52
400 mg COL-144	99	70	68	53
Total	512	391	378	297

[a] Primary analysis population.
ITT = intention-to-treat, mITT = modified intention-to-treat, N = number of patients, PP = per-protocol analyis set, SAF = safety analysis set.

Diagnosis and criteria for inclusion

1. Patients with migraine with or without aura fulfilling the International Headache Society (IHS) diagnostic criteria 1.1 and 1.2.1 (2004)*
2. History of migraine for at least one year
3. Migraine onset before the age of 50 years
4. History of 1 - 8 migraine attacks per month
5. Male or female patients aged 18 to 65 years
6. Female patients of childbearing potential with a highly effective form of contraception (e.g. combined oral contraceptive, intrauterine device, abstinence, vasectomized partner)
7. Able and willing to give written informed consent

* Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders (second edition). Cephalalgia. 2004; 24; Suppl 1:1-160

8. Able and willing to complete a migraine diary card to record details of the attack treated with study medication

Exclusion criteria

1. History of life threatening or intolerable adverse reaction to any triptan
2. Use of prescription migraine prophylactic drugs within 15 days (30 days for flunarizine) prior to screening and during study participation
3. Use of herbal preparations (e.g. feverfew, butterbur) for migraine prophylaxis
4. Use of 5-HT reuptake inhibitors
5. Use of drugs known to cause significant inhibition of cytochrome P450
6. Pregnant or breast-feeding women
7. Women of childbearing potential who were not using highly effective contraception
8. History or evidence of coronary artery disease, ischemic or hemorrhagic stroke, epilepsy or any other condition placing the patient at increased risk of seizures*
9. History of or current hypertension (controlled or uncontrolled)
10. History of orthostatic hypotension with syncope
11. Current use of hemodynamically active cardiovascular drugs
12. History within the previous three years or current evidence of abuse of any drug, prescription or illicit, or alcohol
13. Significant renal or hepatic impairment
14. Previous participation in this clinical trial
15. Participation in any clinical trial of an experimental drug or device in the previous 30 days
16. Any medical condition or laboratory test which in the judgment of the investigator made the patient unsuitable for the study
17. Known Hepatitis B or C or human immunodeficiency virus infection
18. Patients who were employees of the sponsor
19. Relatives of, or staff directly reporting to, the investigator
20. Patients with known hypersensitivity to COL-144, other 5-HT_{1F} receptor agonists or any excipient of COL-144 drug product
21. Patients who were treated with study medication in the COL MIG-201 study (patients screened but not treated under that protocol were not excluded)

IMP, dose, mode of administration and batch

COL-144 tablets (50 mg or 200 mg), single dose, oral administration, lot numbers CCI (50 mg active) and CCI (200 mg active). Each patient received a combination of four active or matching placebo tablets (two medium and two small) to give a total dose of 0, 50, 100, 200 or 400 mg of COL-144.

* In France, peripheral arterial pathology was also excluded (see country-specific amendment in Section 9.8).

Reference product, dose, mode of administration and batch

Placebo tablets, single oral administration, lot numbers CCI (50 mg placebo) and CCI (200 mg placebo).

Duration of treatment

Single administration

Criteria for evaluation

Efficacy

Primary endpoint

- Headache response (defined as reduction in headache severity from moderate or severe at baseline to mild or none 2 hours post-dose)

Secondary endpoints

- Headache-free 2 hours post-dose
- Headache severity (at 0.5, 1, 1.5, 2, 3, 4 and 24 hours post-dose)
- Headache recurrence within 24 hours post-dose
- Presence or absence of nausea, phonophobia, photophobia, and vomiting (at 0.5, 1, 1.5, 2, 3, 4 and 24 hours post-dose)
- Clinical disability (at 0.5, 1, 1.5, 2, 3, 4 and 24 hours post-dose)
- Requirement for rescue medication between 2 and 24 hours post-dose
- Patient global impression at 2 hours post-dose
- Time to meaningful pain relief and time to pain free

Further efficacy endpoints defined in the statistical analysis plan (SAP)

- Headache response at 0.5, 1, 1.5, 3, 4 and 24 hours post-dose
- Headache-free at 0.5, 1, 1.5, 3, 4 and 24 hours post-dose
- Sustained response at 24 hours post-dose
- Sustained pain free at 24 hours and 48 hours post-dose
- Use of rescue medication within 48 hours post-dose

Safety

- AEs (spontaneously reported)
- 12-lead ECGs
- Vital signs
- Clinical laboratory parameters
- Physical examination

Statistical methods

The primary efficacy endpoint, headache response 2 hours post-dose, was analyzed using a hierarchical test procedure. The Cochran-Armitage test for trend was used to evaluate a linear association between response rate and dose. If significant, individual between-treatment differences were analyzed with Pearson's chi-square tests starting with comparison of placebo with the highest dose of COL-144 (400 mg). Subsequent tests were performed in the following order: placebo vs 200 mg COL-144, placebo vs 100 mg COL-144, 50 mg COL-144 vs 400 mg COL-144 and placebo vs 50 mg COL-144 and were only carried out if the previous test was statistically significant.

The primary efficacy endpoint was analyzed based on the modified intention-to-treat (mITT), intention-to-treat (ITT) and per-protocol (PP) populations. Analysis of the primary efficacy endpoint using the mITT population was considered confirmatory. Patients in the ITT population who treated absent or mild headache, who did not provide a headache severity rating at baseline, who used other medication prior to the study medication for the study migraine attack, or who did not consume all four study medication tablets were excluded from the mITT population.

All other analyses were considered exploratory and were based on the mITT and the PP population. The Cochran-Armitage test was used to test for a linear association of response rates with COL-144 dose. Pearson's chi-square was used to compare the proportions of patients and Cochran-Mantel-Haenszel (CMH) mean score tests were used to compare the mean scores in the placebo group with each dose of COL-144. Ordinal variables were analyzed using the CMH correlation test for correlation of response with dose of COL-144. Time to pain relief and time to pain free analyses were performed with Kaplan-Meier methods and treatment groups were compared using the log-rank test. All statistical tests were based on a 2-sided 5% level of significance.

In all efficacy analyses a conservative approach was adopted whereby a patient who used rescue medication was treated as "failure" at all subsequent timepoints (worst case scenario analysis).

AEs, laboratory parameters, vital signs, ECG and physical examination findings were summarized descriptively.

A total sample size of 330 evaluable patients (66 per group without dropouts) was calculated to be required in order to provide 90% power for the primary efficacy analysis, based on a 2-sided test at the 5% level of significance.

SUMMARY OF RESULTS

Patient disposition

Of 534 patients screened, 512 patients were randomized to receive either placebo or one of the four COL-144 doses. A total of 391 patients used study medication. One patient was lost to follow-up and did not terminate the study. The remaining 390 patients terminated the study as planned.

Demographics and baseline characteristics

Demographic and screening characteristics were broadly comparable between the treatment groups. Most patients were Caucasian females. The median ages in the treatment groups ranged from 40 to 45 years. Weight, height and BMI were comparable across the treatment groups.

Characteristics of the treated migraine attack

Median time to dosing from start of the acute migraine attack was 2.2 hours in the placebo and 1.8 to 2.8 hours in the COL-144 groups. Median time to dosing from start of severe to moderate pain was approximately 0.2 hours in all treatment groups. A severe migraine attack was reported by approximately 40% of patients in the placebo, 50 mg, 100 mg and 400 mg COL-144 groups, while the proportion of patients was somewhat higher in the 200 mg COL-144 group (47.9%). The migraine attack caused marked interference with normal activities in most patients in all treatment groups.

Results

Efficacy

Primary endpoint

At 2 hours post-dose a higher proportion of patients experienced a headache response in all COL-144 groups (43.0% at 50 mg to 64.7% at 400 mg) compared to placebo (25.9%). A significant linear association between headache response rates and COL-144 doses was shown ($p < 0.0001$). The hierarchical test procedure was continued and differences in headache response rates between the placebo and each COL-144 dose group, as well as between the 50 mg and 400 mg COL-144 dose group, were statistically significant ($p < 0.05$ for all comparisons).

Secondary endpoints

Headache-free: The proportion of patients headache-free at 2 hours post-dose was 7.4% in the placebo group and ranged from 13.6% (100 mg) to 27.9% (400 mg) in the COL-144 groups. There was a statistically significant linear trend between headache-free rates and COL-144 dose ($p = 0.0006$).

Headache severity: The proportion of patients with moderate or severe headache decreased in all treatment groups up to 2 hours post-dose. The decrease was smaller in the placebo group than in the COL-144 groups ($p < 0.03$). At each time point a statistically significant linear correlation between headache severity and COL-144 dose was shown.

Headache recurrence: The proportion of patients with headache recurrence (moderate or severe headache at baseline, which became mild or none at 2 hours post-dose and worsened again up to 24 hours post-dose) was lowest in the 400 mg COL-144 group (50.0%) and ranged from 50% to 63% across all treatment groups. There was no significant linear trend between headache recurrence rate and treatment group.

Nausea, phonophobia, photophobia and vomiting

Generally, the number of patients with nausea, phonophobia, photophobia or vomiting decreased up to 2 hours after COL-144 treatment, but appeared to increase at later time points. However, after 2 hours post-dose, patients taking rescue medication were counted as having nausea, phonophobia, photophobia or vomiting, most likely leading to an overestimation of the number of patients with these symptoms after 2 hours.

Nausea: There was a statistically significant linear trend between the proportion of patients with nausea and COL-144 dose at all time points starting from 3 hours post-dose up to 24 hours ($p < 0.02$). The proportion of patients with nausea decreased up to 2 hours post-dose in all treatment groups, with the smallest decrease observed in the placebo group. After 2 hours post-dose the proportion of patients with nausea again increased as described above.

Phonophobia and photophobia: A statistically significant linear trend between the proportion of patients with photophobia and phonophobia and COL-144 dose was seen at 1.5 and 2 hours post-dose up to 24 hours post-dose, respectively ($p < 0.04$). The proportion of patients with phonophobia or photophobia decreased in all treatment groups up to 2 hours post-dose, with the smallest decrease observed in the placebo group. After 2 hours post-dose the proportion of patients with phonophobia tended to increase again, while photophobia remained relatively stable. The increase in phonophobia at later time points is most likely an overestimation as described above.

Vomiting: A statistically significant linear trend for a decrease in vomiting and increasing dose of COL-144 was seen at 1.5 hours, and from 3 until 24 hours post-dose ($p < 0.007$). The proportion of patients with vomiting at baseline was low (9% in the placebo and 0% to 2.5% in the COL-144 groups) and there was almost no change during the first 2 hours post-dose in any treatment group. The number of patients with vomiting then appeared to increase at later time points in all treatment groups, most likely an overestimation as noted above.

Clinical disability: Starting from 2 hours post-dose, there was a statistically significant linear association between clinical disability and dose of COL-144 up to 24 hours ($p < 0.01$). Severity of clinical disability decreased with increasing doses of COL-144.

Requirement for rescue medication: The proportion of patients who used rescue medication between 2 and 24 hours post-dose was higher in the placebo group (68.8%) than in the COL-144 groups (41.8% to 61.2%). There was a significant linear association between the decreased proportion of patients who took rescue medication and increasing dose of COL-144 ($p = 0.0093$).

Patient global impression: The proportion of patients who reported feeling much better or very much better 2 hours post-dose was higher in the COL-144 groups compared to placebo. There was a statistically significant linear association between patient global impression and increasing dose of COL-144 ($p = 0.0162$). Patient global impression improved with increasing doses of COL-144.

Time to meaningful pain relief and time to pain free: The time to meaningful pain relief was shortest in the 400 mg COL-144 group (155 minutes) and longest in the placebo group (1095 minutes). The time to pain free was shortest in the 400 mg COL-144 group (400 minutes) and longest in the placebo group (median not reached by the end of the study). The log-rank test revealed a statistically significant difference among the treatment groups for time to pain relief and time to pain free ($p < 0.002$).

Safety

No patients died during this study. An SAE of dizziness was experienced by one patient in the 200 mg COL-144 group. This SAE was considered to be probably related to the study medication, was of moderate intensity and resolved without sequelae.

A total of 680 AEs were reported by 266 of 391 patients (68.0%). The proportion of patients reporting at least one AE was higher in the COL-144 groups (68% to 87%) than in the placebo group (31%). Within the COL-144 groups, the proportion of patients that reported at least one AE was lowest in the 50 mg group compared to other dose groups and was highest in the 200 mg and 400 mg COL-144 groups.

Overview of adverse events (SAF, N = 391)

		COL-144			
	Placebo	**50 mg**	**100 mg**	**200 mg**	**400 mg**
Number of AEs	37	127	172	162	182
Number of TEAEs	26	110	154	148	171
Number of SAEs	-	-	-	1	-
Number (%) of patients with AEs	27 (31.4)	56 (68.3)	60 (73.2)	62 (87.3)	61 (87.1)
Number (%) of patients with TEAEs	19 (22.1)	53 (64.6)	59 (72.0)	61 (85.5)	59 (84.3)
Number (%) of patients with SAEs	-	-	-	1 (1.4)	-

AE = adverse event, N = number of patients, SAE = serious adverse event, SAF = safety analysis set, TEAE = treatment-emergent AE (AEs with a possible, probable or definite relationship to the study medication).

The most frequently experienced AEs in all treatment groups were related to “nervous system disorders”, followed by “general disorders and administration site conditions”. The most frequently reported AEs in all COL-144 groups were dizziness and fatigue, while these AEs were reported by only one or two patients in the placebo group. The majority of events of dizziness and fatigue were treatment-emergent.

Adverse events reported by ≥5% of patients in any treatment group (SAF, N = 391)

System organ class Preferred term (MedDRA)	Number (%) of patients				
		COL-144			
	Placebo (N = 86)	50 mg (N = 82)	100 mg (N = 82)	200 mg (N = 71)	400 mg (N = 70)
Ear and labyrinth disorders	**3 (3.5)**	**8 (9.8)**	**14 (17.1)**	**13 (18.3)**	**18 (25.7)**
Vertigo	1 (1.2)	8 (9.8)	12 (14.6)	12 (16.9)	17 (24.3)
Gastrointestinal disorders	**3 (3.5)**	**10 (12.2)**	**12 (14.6)**	**9 (12.7)**	**13 (18.6)**
Nausea	- -	4 (4.9)	9 (11.0)	3 (4.2)	5 (7.1)
General disorders and administration site conditions	**5 (5.8)**	**22 (26.8)**	**32 (39.0)**	**22 (31.0)**	**26 (37.1)**
Asthenia	- -	4 (4.9)	7 (8.5)	3 (4.2)	4 (5.7)
Fatigue	2 (2.3)	10 (12.2)	17 (20.7)	15 (21.1)	17 (24.3)
Musculoskeletal and connective tissue disorders	**3 (3.5)**	**8 (9.8)**	**10 (12.2)**	**11 (15.5)**	**9 (12.9)**
Muscular weakness	- -	3 (3.7)	5 (6.1)	4 (5.6)	3 (4.3)
Sensation of heaviness	1 (1.2)	4 (4.9)	4 (4.9)	7 (9.9)	5 (7.1)
Nervous system disorders	**8 (9.3)**	**35 (42.7)**	**39 (47.6)**	**46 (64.8)**	**42 (60.0)**
Dizziness	1 (1.2)	19 (23.2)	23 (28.0)	27 (38.0)	26 (37.1)
Paresthesia	2 (2.3)	2 (2.4)	9 (11.0)	12 (16.9)	14 (20.0)
Somnolence	2 (2.3)	8 (9.8)	10 (12.2)	8 (11.3)	8 (11.4)
All AEs	**27 (31.4)**	**56 (68.3)**	**60 (73.2)**	**62 (87.3)**	**61 (87.1)**

All AEs are listed which were reported by at least 5% of patients in any treatment group. The number of patients for a system organ class also includes those AEs which were reported by less than 4 patients.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, SAF = safety analysis set.

A total of 102 severe AEs were reported during this study. A dose-related increase in the number of severe AEs and the proportion of patients reporting at least one severe AE was observed (5.8%, 19.5%, 26.8%, 39.4% and 44.3% of patients).

No clinically meaningful changes in hematology, clinical chemistry or urinalysis parameters were observed. There was a small number of patients with isolated clinically significant findings without any apparent dose-relationship. There were virtually no changes in vital signs or ECG parameters in any treatment group. A few patients presented with physical examination findings that were reported as AEs; these did not show any dose-relationship.

Conclusions:

- The proportion of patients with headache response at 2 hours post-dose was significantly higher in all COL-144 dose groups compared to placebo.
- Headache response was linearly related to the dose of COL-144.
- Secondary endpoints also showed dose-dependent improvements with COL-144 compared to placebo.

- The number of patients with AEs was higher in all COL-144 groups compared to placebo, with the 200 mg and 400 mg dose showing the highest incidence.
- The most common AEs associated with COL-144 treatment were nervous-system related and included dizziness and fatigue.
- This study showed that COL-144 is effective and well tolerated in the acute treatment of migraine following oral administration.

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