Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial

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Summary

Background **Calcitonin gene-related peptide (CGRP) probably has a role in migraine pathophysiology, and antagonism of its receptors might provide treatment without the vasoconstrictor effects of triptans. We aimed to assess the clinical profile of MK-0974 (telcagepant), an orally bioavailable antagonist of CGRP receptor.**

Methods **In a randomised, parallel-treatment, placebo-controlled, double-blind, trial at 81 sites in the Europe and the USA, adults with migraine diagnosed by International Headache Society criteria treated moderate or severe attacks with either oral telcagepant 150 mg or 300 mg, zolmitriptan 5 mg, or placebo. The five co-primary endpoints were pain freedom, pain relief, or absence of photophobia, phonophobia, or nausea at 2 h after treatment. Analysis was by the full analysis set and multiplicity was controlled for with a step-down closed-testing procedure. This trial is registered with ClinicalTrials.gov, number NCT00442936.**

Findings **1380 patients were randomly assigned to receive telcagepant 150 mg (n=333) or 300 mg (354), zolmitriptan (345), or placebo (348). Telcagepant 300 mg was more effective than placebo for pain freedom (95 [27%] of 353 patients *vs* 33 [10%] of 343 [p<0·0001]), pain relief (194 [55%] of 353 *vs* 95 [28%] of 343 [p<0·0001]), and absences of phonophobia (204 [58%] of 353 *vs* 126 [37%] of 342 [p<0·0001]), photophobia (180 [51%] of 353 *vs* 99 [29%] of 342 [p<0·0001]), and nausea (229 [65%] of 352 *vs* 189 [55%] of 342 [p=0·0061]). Efficacy of telcagepant 300 mg and zolmitriptan 5 mg were much the same, and both were more effective than telcagepant 150 mg. Adverse events were recorded for 31% taking telcagepant 150 mg, 37% taking telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo.**

Interpretation **Telcagepant 300 mg is effective as an acute treatment for migraine with efficacy comparable to that of zolmitriptan 5 mg, but with fewer associated adverse effects.**

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Introduction

Migraine is a common disease and a leading cause of disability.[1] Triptans, agonists of the serotonin receptor 5-$HT_{1B/1D}$, are currently viewed as the best acute migraine-specific treatments, although some patients respond poorly or are unresponsive.[2,3] Generally well tolerated, triptans can be associated with side-effects such as dizziness, paraesthesia, throat tightness, and chest discomfort (not thought to be of cardiac origin in most patients),[4] which can cause some patients to discontinue or change treatment.[5,6] Furthermore, because of potential vasoconstrictor effects, triptans are contraindicated in patients with substantial underlying cardiovascular disease, uncontrolled hypertension, and certain migraine subtypes, including hemiplegic and basilar-type migraine.[4,7] Hence, new treatments for migraine are needed for people who do not respond well to current therapies or who are at substantial risk of cardiovascular disease.

Calcitonin gene-related peptide (CGRP) is a neuropeptide thought to have a key role in the pathophysiology of migraine.[8–10] CGRP concentrations in the cranial circulation may be increased during a migraine attack[11] and CGRP given intravenously triggers a migraine-like headache in people who have migraines.[12] CGRP receptors are found throughout the trigeminal pathways involved in migraine headache pain and have been localised to primary sensory neurons in the trigeminal ganglion, central second-order pain-relay neurons in the trigeminal nucleus caudalis, and smooth muscle cells of the meningeal vasculature.[13,14] Antagonism of these receptors has thus become an important target for new migraine treatments. Since antagonists of CGRP receptor do not seem to have direct vasoconstrictor properties, they might be free of the cardiovascular concerns associated with triptans.[15]

An initial proof-of-concept study reported that an intravenous formulation of the CGRP receptor antagonist BIBN4096BS (olcegepant), was effective and well-tolerated in the acute treatment of migraine.[16] Because most migraine attacks are treated on an outpatient basis, intravenous formulations are not

practically or commercially viable as acute treatments, and oral CGRP antagonists are needed. MK-0974 (telcagepant) is an oral CGRP receptor antagonist being investigated in clinical trials.[17–19] The initial phase II proof-of-concept study used an adaptive dose-ranging design to assess the efficacy and safety of doses from 25 mg to 600 mg.[19] All doses were well-tolerated. Doses of 300 mg to 600 mg were more effective than placebo and had efficacy comparable to the established triptan rizatriptan.

The primary aim of this study was to confirm the efficacy and safety profile of telcagepant compared with those of placebo and a triptan in the acute treatment of migraine in a large phase III trial. The phase II study suggested that the efficacy of telcagepant doses between 300 mg and 600 mg were comparable. The 300 mg dose was chosen as the primary dose for further investigation. A 150 mg dose was selected as a second dose in this study to further define the dose–response curve. Zolmitriptan 5 mg (the maximum recommended dose in the USA) was chosen as an active comparator because it is among the most widely used and effective of the oral triptan treatments.[2]

Assessment of effects on migraine symptoms focused on the 2 h time point, which is the standard time point recommended for migraine trials.[20] Sustained efficacy measures, which assess duration of response over longer periods while accounting for headache recurrence and the use of rescue drugs, were also assessed.[20] Results of previous studies with olcegepant and telcagepant, showed that CGRP receptor antagonists might be more effective than triptans on sustained measures.

Methods

Study population and design

Patients were recruited from primary care and headache centres. Patients were eligible for the study if they were ≥18 years of age, had a history of migraine for at least 1 year, and in the 2 months prior to the screening visit had had one to eight moderate or severe migraine attacks per month with or without aura (International Headache Society criteria)[21] that typically lasted 4–72 h untreated. Patients were required to have good general health. Patients with a history or clinical evidence of either cardiovascular disease or uncontrolled hypertension were excluded because zolmitriptan is

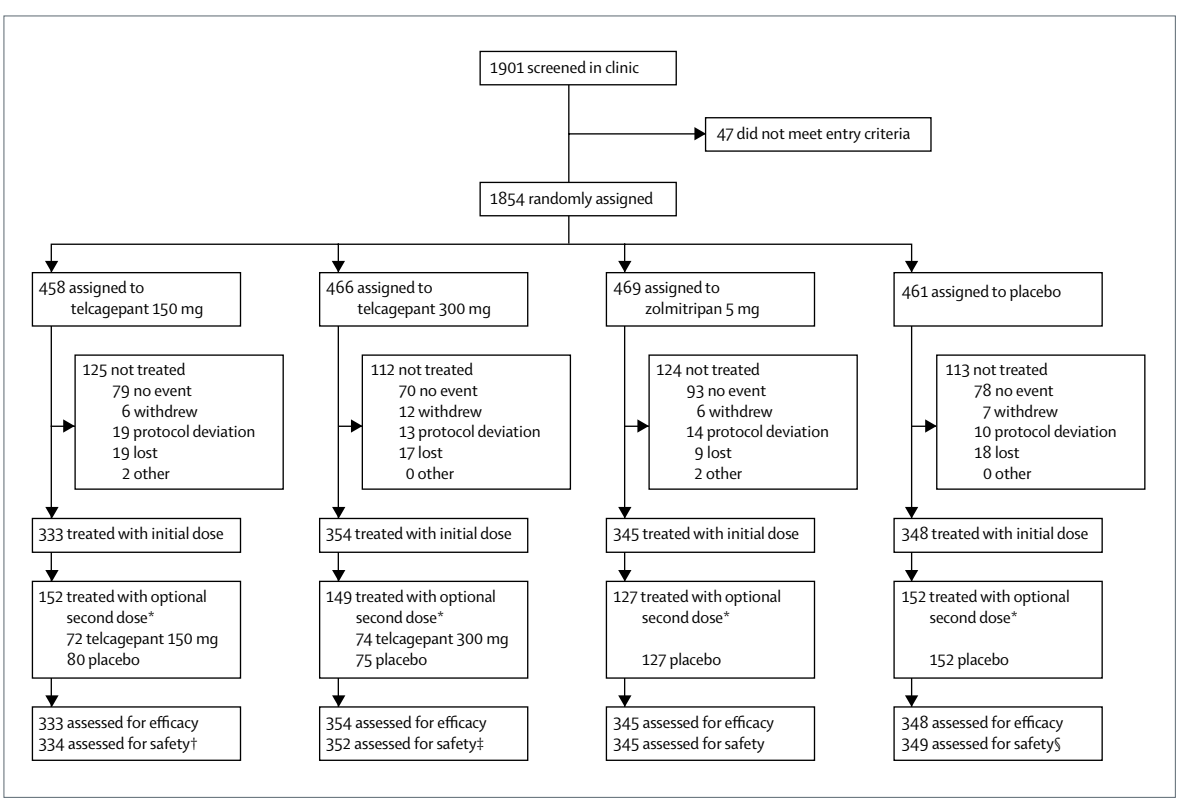

Figure 1: **Trial profile**

*Patients had the option of taking a masked second dose of study drug if migraine was still moderate or severe at 2 h or for headache recurrence within 48 h. †One more than the number who treated with the initial dose because a patient allocated to telcagepant 150 mg (initial dose) and placebo (optional second dose) gave her study medication to her sister who was also in the study (the sister was allocated to telcagepant 300 mg initial dose and optional second dose, but took telcagepant 150 mg and placebo instead). ‡Two fewer than the number treated with the initial dose because of the sister assigned to telcagepant 300 mg who actually took telcagepant 150 mg, and another patient who only took an optional second dose of placebo. §One more than the number treated with the initial dose because one patient took only the optional second dose.

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contraindicated in these patients. Patients taking migraine prevention medication were allowed to enter the study provided that their prescribed daily dose had not changed during the 3 months before screening. Patients taking potent CYP3A4 inhibitors or inducers, serotonin norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or propranolol within 1 month of the screening visit were not eligible, and these drugs were not permitted during the study. Potent inhibitors or inducers of CYP3A4 were prohibited because of potential interactions with telcagepant. Serotonin norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and propranolol were prohibited because of potential interactions with zolmitriptan.[22] The study was approved by the appropriate ethical-review committee for each site and each patient provided written informed consent.

This was a randomised, double-blind, placebo-controlled and active-controlled, parallel-group, outpatient study to assess the efficacy and tolerability of telcagepant in patients with an acute migraine attack. The study (Merck Research Laboratories Protocol 011) was done at 81 sites in the Europe and the USA from February, 2007, to October, 2007, inclusive. Patients were allocated in equal ratios to either telcagepant 150 mg, telcagepant 300 mg, zolmitriptan 5 mg, or placebo. Patients took study medication when they had a moderate or severe migraine attack. Patients had the option of taking a blinded optional second dose of study medication if they still had a moderate or severe migraine attack 2 h after dosing or if headache recurred within 48 h of the initial dose. Patients who were randomly assigned to either zolmitriptan or placebo as their initial treatment were allocated to receive placebo for their optional second dose, while those initially assigned to telcagepant were allocated to receive a second dose of telcagepant or placebo in equal ratio. The efficacy of the optional second dose is not discussed here since the sample sizes were limited. A prespecified meta-analysis across all of the telcagepant phase III studies is planned to address the therapeutic effect of the second dose. Telcagepant was supplied as a liquid-filled soft elastic capsule formulation (with matching placebo) and zolmitriptan was supplied as a single 5 mg tablet (with matching placebo). Each study treatment was packaged with a triple dummy design (eg, patients assigned to telcagepant 150 mg also received placebo matching telcagepant 300 mg and placebo matching zolmitriptan 5 mg). The formulation of telcagepant used in this study reached its maximum concentration in 1–2 h and had an elimination half-life of about 5–8 h. The final clinical formulation will likely be a tablet, with pharmacokinetic properties much the same as this capsule formulation. Patients were allocated to treatment by a computer-generated randomised schedule prepared by a blinded statistician at Merck Research Laboratories, with a block size of eight patients. Numbered containers were used to implement allocation. Personnel at each study site used a central interactive voice response system to determine which container should be given to which patient. All study personnel, including investigators, study-site personnel, patients, and monitors and statisticians from Merck remained unaware of treatment allocation throughout the study; unblinding took place after data collection was complete.

Patients attended a screening visit during which eligibility was assessed and physical examinations, laboratory screens, and electrocardiography were done. Eligible patients were enrolled and provided with study treatment to be taken on an outpatient basis as soon as they had moderate or severe migraine headaches. If patients still had moderate or severe migraine 2 h after dosing, or if headache recurred 2–48 h after dosing, they could take a blinded optional second dose of study treatment (see above) or take their own rescue medication (with the provisos that triptan use was restricted to zolmitriptan and that ergot derivatives were not allowed).

	Telcagepant 150 mg (n=333)	Telcagepant 300 mg (n=354)	Zolmitriptan 5 mg (n=345)	Placebo (n=348)
Patients				
Mean age (SD), years	42·7 (11·2)	42·6 (11·4)	41·7 (12)	42·3 (12)
Women	277 (83%)	300 (85%)	298 (86%)	294 (84%)
White	319 (96%)	340 (96%)	326 (94%)	324 (93%)
Using prophylaxis	55 (17%)	46 (13%)	59 (17%)	53 (15%)
Usual acute migraine treatment				
None	11 (3%)	6 (2%)	7 (2%)	4 (1%)
NSAID	94 (28%)	72 (20%)	86 (25%)	99 (28%)
Triptan	144 (43%)	168 (47%)	154 (45%)	148 (43%)
NSAID and triptan	59 (18%)	70 (20%)	63 (18%)	66 (19%)
Other	25 (8 %)	38 (11%)	34 (10%)	31 (9%)
Baseline characteristics of treated attack				
Aura	55 (17%)	59 (17%)	63 (18%)	67 (19%)
Moderate headache	200 (60%)	216 (61%)	222 (64%)	218 (63%)
Severe headache	131 (39%)	138 (39%)	121 (35%)	127 (36%)
Phonophobia	230 (70%)	250 (71%)	246 (73%)	261 (76%)
Photophobia	266 (82%)	283 (80%)	270 (79%)	292 (85%)
Nausea	182 (55%)	201 (57%)	191 (56%)	200 (58%)
Vomiting	18 (6%)	32 (9%)	19 (6%)	18 (5%)
Baseline function for treated attack				
Normal	14 (4%)	16 (5%)	9 (3%)	12 (3%)
Mildly impaired	182 (55%)	179 (51%)	194 (56%)	176 (51%)
Severely impaired	99 (30%)	133 (38%)	108 (31%)	114 (33%)
Requiring bedrest	35 (11%)	26 (7%)	32 (9%)	43 (12%)

Values are number (%) unless otherwise stated. n=number of treated patients. Sample sizes differed slightly from this number for some characteristics because of missing data. Thus, some percentages do not add up to 100% (eg, the different categories of baseline function) due to missing data.

Table 1: **Characteristics of patients and treated migraine attacks at baseline**

	Odds ratio (95% CI)*	p value
Telcagepant 300 mg *vs* placebo: pain freedom 2 h	3·55 (2·31–5·47)	<0·0001†
Telcagepant 300 mg *vs* placebo: pain relief 2 h	3·39 (2·45–4·67)	<0·0001†
Telcagepant 300 mg *vs* placebo: no phonophobia 2 h	2·43 (1·78–3·30)	<0·0001†
Telcagepant 300 mg *vs* placebo: no photophobia 2 h	2·60 (1·90–3·57)	<0·0001†
Telcagepant 300 mg *vs* placebo: no nausea 2 h	1·54 (1·13–2·10)	0·0061†
Telcagepant 300 mg *vs* placebo: 2–24 h sustained pain freedom	5·04 (2·89–8·78)	<0·0001†
Telcagepant 300 mg *vs* zolmitriptan 5 mg: 2–24 h sustained pain freedom	1·18 (0·80–1·73)	0·3985
Telcagepant 150 mg *vs* placebo: pain freedom 2 h	2·00 (1·26–3·17)	0·0031‡
Telcagepant 150 mg *vs* placebo: pain relief 2 h	2·75 (1·99–3·81)	<0·0001‡
Telcagepant 150 mg *vs* placebo: no phonophobia 2 h	2·06 (1·51–2·82)	<0·0001‡
Telcagepant 150 mg *vs* placebo: no photophobia 2 h	2·05 (1·49–2·83)	<0·0001‡
Telcagepant 150 mg *vs* placebo: no nausea 2 h	1·69 (1·23–2·32)	0·0012‡
Telcagepant 150 mg *vs* placebo: 2–24 hour sustained pain freedom	2·35 (1·29–4·30)	0·0054‡
Telcagepant 150 mg *vs* zolmitriptan 5 mg: 2–24 h sustained pain freedom	0·55 (0·35–0·86)	0·0092‡
Telcagepant 300 mg *vs* zolmitriptan 5 mg: pain freedom 2 h	0·83 (0·59–1·15)	0·2597
Telcagepant 150 mg *vs* zolmitriptan 5 mg: pain freedom 2 h	0·47 (0·32–0·67)	<0·0001‡

Odds ratio greater than 1 favours the first treatment. *From logistic model adjusting for geographic region, baseline migraine severity, and age. †Statistically significant at α=0·05 under prespecified closed testing procedure. ‡Nominally statistically significant at α=0·05 (a positive result cannot be formally claimed).

Table 2: **Summary of hypothesis testing with closed testing procedure**

Data collection

During the 48 h after the initial dose of study medication, patients recorded subjective assessments of migraine symptoms and use of any rescue medication in a paper diary. Patients also recorded information about any adverse events that occurred up to the time they returned to the clinic. Patients were instructed to return to the study site within about 7 days of treatment for review of the diary, assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography).

Headache severity was recorded using a four-grade scale (no pain, mild pain, moderate pain, severe pain) at baseline (time of taking study drug) and at 0·5, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0, 6·0, 8·0, and 24·0 h after. The presence or absence of associated symptoms (nausea, vomiting, photophobia, or phonophobia) and ratings of functional disability (four-grade scale: normal, mildly impaired, severely impaired, requires bedrest) were recorded at the same time points as the headache severity ratings. For those patients who had pain relief (reduction of pain to mild or none) or pain freedom (no pain) at 2 h, presence or absence of headache worsening (recurrence) within 2–24 h and 24–48 h was recorded. Use of rescue medication (including the optional second dose) within 48 h was also recorded. Patients also completed the migraine-specific quality-of-life questionnaire[23] 24 h after dosing.

Tolerability and safety were assessed with reports of spontaneous adverse events and routine prestudy and post-study physical and laboratory testing, including electrocardiography.

Statistical analysis

The full-analysis-set (FAS) was the primary population for assessing efficacy. For each primary endpoint, the FAS included all treated patients who had a baseline headache severity score and at least one postdose measurement occurring at or before 2 h after taking the drug. Non-baseline missing data were imputed using a last-observation-carried forward approach. Patients were counted in the treatment group to which they were randomly assigned. Patients who took the initial telcagepant dose (150 mg or 300 mg) were considered to be a part of the same treatment group (150 mg or 300 mg) regardless of the optional second dose.

The five co-primary hypotheses were that at least one telcagepant dose would be superior to placebo in the treatment of migraine, as measured by the percentage of patients reporting pain freedom, pain relief, absence of photophobia, absence of phonophobia, and absence of nausea at 2 h. On the basis of a sample size of 450 patients randomly assigned per treatment group (assumed to yield 382 evaluable patients per treatment group) and using a one-sided significance level of 0·025, the study had at least 90% power to show significance on the five co-primary endpoints.

Secondary endpoints were 2–24 h sustained pain freedom (pain free from 2–24 h without the use of rescue medication, including the optional second dose); total migraine freedom at 2 h (no pain and no associated symptoms of photophobia, phonophobia, nausea, or vomiting); and 2–24 h total migraine freedom (2–24 h sustained pain freedom with no associated symptoms from 2–24 h). 2–24 h sustained pain freedom was the key secondary endpoint.

The response rates and odds ratios in all study groups were estimated with a logistic model with categorical terms for treatment, geographic region (Europe or USA), and baseline headache severity (moderate or severe), with age included as a continuous covariate. To control for multiplicity, a step-down closed testing procedure[24] was applied to the five co-primary hypotheses and the secondary hypotheses, each at a significance level of 0·05. All planned treatment comparisons pertaining to the primary and secondary hypotheses (which involved comparisons of telcagepant to placebo and telcagepant to zolmitriptan) were done, even if a preceding comparison, per the step-down closed testing procedure, failed to achieve formal statistical significance; p values less than 0·05 for these hypothesis tests are said to be nominally significant.

This report focuses on the prespecified primary and secondary analyses. Additional prespecified exploratory analyses were done involving the above measures at additional time points (pain freedom, pain relief, and absence of associated symptoms at time points other than 2 h, 2–48 h sustained pain freedom) or different measures (functional disability, migraine quality-of-life, 2–24 h and 2–48 h sustained pain relief, headache

	Telcagepant 150 mg (n=333)		Telcagepant 300 mg (n=354)		Zolmitriptan 5 mg (n=345)		Placebo (n=348)
	Efficacy	p value	Efficacy	p value	Efficacy	p value	Efficacy
Primary							
Pain freedom 2 h	57/331 (17·2%; 13·3–21·7)	0·0031*	95/353 (26·9%; 22·4–31·9)	<0·0001	107/342 (31·3%; 26·4–36·5)	<0·0001	33/343 (9·6%; 6·7–13·2)
Pain relief 2 h	165/331 (49·8%; 44·3–55·4)	<0·0001	194/353 (55·0%; 49·6–60·2)	<0·0001	193/342 (56·4%; 51·0–61·8)	<0·0001	95/343 (27·7%; 23·0–32·8)
No phonophobia 2 h	178/331 (53·8%; 48·2–59·2)	<0·0001	204/353 (57·8%; 52·4–63·0)	<0·0001	188/340 (55·3%; 49·8–60·7)	<0·0001	126/342 (36·8%; 31·7–42·2)
No photophobia 2 h	149/331 (45·0%; 39·6–50·6)	<0·0001	180/353 (51·0%; 45·6–56·3)	<0·0001	171/342 (50·0%; 44·6–55·4)	<0·0001	99/342 (28·9%; 24·2–34·1)
No nausea 2 h	221/330 (67·0%; 61·6–72·0)	0·0012	229/352 (65·1%; 59·8–70·0)	0·0061	243/341 (71·3%; 66·1–76·0)	<0·0001	189/342 (55·3%; 49·8–60·6)
Secondary							
2–24 h sustained pain freedom	35/328 (10·7%; 7·5–14·5)	0·0054†	71/351 (20·2%; 16·1–24·8)	<0·0001	62/341 (18·2%; 14·2–22·7)	<0·0001	17/343 (5·0%; 2·9–7·8)
Total migraine freedom 2 h	44/331 (13·3%; 9·8–17·4)	0·0515*	81/353 (22·9%; 18·7–27·7)	<0·0001	93/342 (27·2%; 22·5–32·2)	<0·0001	30/343 (8·7%; 6·0–12·3)
2–24 h total migraine freedom	27/329 (8·2%; 5·5–11·7)	0·0543‡	61/351 (17·4%; 13·6–21·8)	<0·0001	54/341 (15·8%; 12·1–20·2)	<0·0001	16/343 (4·7%; 2·7–7·5)

Data are numbers of patients (%; 95% CI). n=number of treated patients; the actual sample sizes in the FAS population differed slightly from n for some endpoints due to missing data. The observed (not model-based) percentages are presented. p values were computed with a logistic model adjusting for baseline severity, geographic region, and age relative to the effect with placebo. No comparisons between telcagepant doses were made. For the telcagepant *vs* zolmitriptan pairwise comparison: *p<0·0001; †p=0·0092; ‡p=0·0041.

Table 3: **Summary of efficacy for primary and secondary endpoints**

recurrence, use of rescue medication, pain-intensity difference, summed pain intensity difference, time to pain freedom, duration of pain freedom). Findings of interest from these analyses are also presented. The full set of findings from exploratory analyses are not reported in this Article as we intend to publish these elsewhere in the future. Exploratory analyses also compared outcomes for zolmitriptan with those for placebo.

All patients who were randomly assigned and took study treatment were included in the safety assessment. All adverse events reported up to 14 days after treatment were included. The proportions of patients with any adverse events, any serious adverse events, and the most commonly occurring adverse events were calculated for each treatment group. In addition, the percentages of patients with a triptan-related adverse event, defined as chest pain, chest tightness, asthenia, paraesthesia, dysaesthesia, or hyperaesthesia, were calculated. To fully characterise the tolerability profile of telcagepant, a separate analysis was also done with adverse events in the first 48 h of dosing (on the assumption that adverse events soon after dosing were those most likely to be attributable to drug).

Role of the funding source

The study was funded by Merck Research Laboratories. The study sponsor was involved in the study design, data collection, data analysis, data interpretation, and the writing of the Article. The initial draft was written by C Lines, T Ho and J Kost from Merck Research Laboratories. All authors had full access to all the data. The corresponding author had final responsibility for submission of the paper.

Results

Figure 1 is the trial profile. A total of 1380 patients were treated. Of these, 850 were from European sites and 530 were from US sites. Table 1 summarises characteristics of the patients taking treatment and the baseline characteristics of treated migraine attacks. The mean age of treated patients was 42·3 years and 85% were women. Most patients usually used a triptan, a non-steroidal anti-inflammatory drug, or both, to treat their migraine attacks. Most treated headaches were not preceded by aura, and were associated with some level of functional disability. The demographic profiles and baseline attack characteristics of the treatment groups were much the same.

Table 2 summarises comparisons for which strong type 1 error control was specified to test the hypotheses. On the basis of this closed testing procedure and the logistic regression model, telcagepant 300 mg was superior to placebo on all five co-primary endpoints at 2 h and on the key secondary endpoint of 2–24 h sustained pain freedom. Because telcagepant 300 mg was not superior to zolmitriptan 5 mg with regard to 2–24 h sustained pain freedom, formal statistical significance cannot be claimed for the remaining comparisons in the step-down closed-testing procedure. This includes all comparisons of telcagepant 150 mg versus placebo.

On the basis of nominal p values, all active treatments were more effective than placebo on the primary endpoints and the key secondary endpoint of 2–24 h sustained pain freedom (table 3). Telcagepant 300 mg and zolmitriptan 5 mg were also more effective than placebo on the other secondary endpoints relating to total migraine freedom. Telcagepant 300 mg and zolmitriptan 5 mg had comparable efficacy and were both slightly more effective than telcagepant 150 mg on most measures, although statistical testing was done only for zolmitriptan versus telcagepant 150 mg and 300 mg (not for telcagepant 300 mg versus 150 mg). A similar pattern of results was observed for the exploratory measures, including sustained pain relief, functional disability, and quality-of-life assessments (table 4).

	Telcagepant 150 mg (n=333)		Telcagepant 300 mg (n=354)		Zolmitriptan 5 mg (n=345)		Placebo (n=348)
	Efficacy	p value	Efficacy	p value	Efficacy	p value	Efficacy
Headache							
2–48 h sustained pain freedom	25/324 (7·7%; 5·1–11·2)	0·0427	64/347 (18·4%; 14·5–22·9)	<0·0001	44/333 (13·2%; 9·8– 17·3)	<0·0001	14/342 (4·1%; 2·3–6·8)
2–24 h sustained pain relief	94/323 (29·1%; 24·2–34·4)	<0·0001	132/350 (37·7%; 32·6–43·0)	<0·0001	122/339 (36·0%; 30·9–41·3)	<0·0001	53/343 (15·5%; 11·8–19·7)
2–48 h sustained pain relief	82/319 (25·7%; 21·0–30·9)	<0·0001	108/345 (31·3%; 26·4–36·5)	<0·0001	95/330 (28·8%; 24·0–34·0)	<0·0001	46/340 (13·5%; 10·1–17·6)
Functional disability 2 h							
Normal	77/331 (23·3%)	0·0130	123/353 (34·8%)	<0·0001	111/342 (32·5%)	<0·0001	55/343 (16·0%)
Mildly impaired	144/331 (43·5%)	..	128/353 (36·3%)	..	135/342 (39·5%)	..	120/343 (35·0%)
Severely impaired	53/331 (16·0%)	..	54/353 (15·3%)	..	45/342 (13·2%)	..	94/343 (27·4%)
Requiring bedrest	57/331 (17·2%)	..	48/353 (13·6%)	..	51/342 (14·9%)	..	74/343 (21·6%)
Migraine quality-of-life 24 h*							
Work functioning	12·0 (0·3)	0·0619	12·4 (0·3)	0·0048	12·6 (0·3)	0·0010	11·4 (0·3)
Social functioning	11·6 (0·3)	0·0091	12·3 (0·3)	<0·0001	12·2 (0·3)	<0·0001	10·6 (0·3)
Energy or vitality	11·2 (0·3)	0·0413	11·9 (0·3)	0·0001	11·8 (0·3)	0·0002	10·5 (0·3)
Migraine symptoms	12·4 (0·3)	0·0316	13·2 (0·2)	<0·0001	13·2 (0·2)	<0·0001	11·7 (0·3)
Feelings or concerns	11·4 (0·3)	0·0247	12·0 (0·3)	<0·0001	12·3 (0·3)	<0·0001	10·6 (0·3)

Data are number of patients (%; 95% CI), number of patients (%), or mean (SE). Actual sample sizes in the FAS population differed slightly from n for some endpoints due to missing data. The observed (not model-based) percentages and corresponding CIs are presented. p values for headache measures and functional disability (dichotomised normal or not normal scale) were computed with a logistic model adjusting for baseline severity, geographic region, and age relative to the effect with placebo. p values for migraine quality-of-life were computed using an ANCOVA model adjusted for geographic region, baseline severity, and age relative to effect with placebo. No comparisons between telcagepant doses were made. For the telcagepant 150 mg *vs* zolmitriptan pairwise comparison: p=0·0321 for 2–48 h sustained pain freedom, p=0·0130 for functional disability, p=0·0363 for migraine symptoms, and p=0·0174 for feelings or concerns. For telcagepant 300 mg *vs* zolmitriptan: p=0·0395 for 2–48 h sustained pain freedom. *The range of scores for each domain is 3–21, high scores indicate better quality-of-life.

Table 4: **Summary of efficacy for selected exploratory endpoints**

All active treatments began to eliminate pain more effectively than placebo starting from about 1 h after the dose (figure 2). The exploratory analysis of 2–48 h sustained pain freedom supports the favourable long-term efficacy of telcagepant, with telcagepant 300 mg having a nominally significant advantage compared with zolmitriptan 5 mg (table 4).

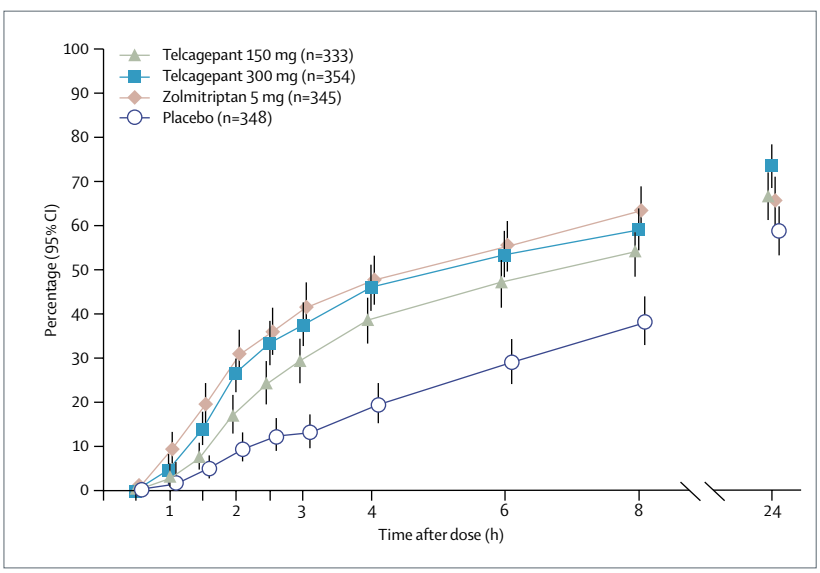

Figure 2: **Observed percentage of patients reporting pain freedom up to 24 h after dosing**
Data were calculated with a last-observation-carried-forward approach to impute missing values, with the proviso that missing baseline values were not imputed. Significant (p≤0·05) differences versus placebo were seen from 1 h for telcagepant 300 mg and zolmitriptan 5 mg, and from 1·5 h for telcagepant 150 mg. Data after 2 h include patients who took an optional second dose or rescue drugs.

Telcagepant and zolmitriptan were generally well-tolerated in the acute treatment of migraine. Most adverse events were in the first 48 h after dosing (table 5). The proportions of patients with adverse events were slightly higher for telcagepant 300 mg than for placebo, and higher for zolmitriptan than for telcagepant 300 mg and 150 mg. Rates of adverse events for telcagepant 150 mg and for placebo were much the same. The grouping of adverse experiences prespecified as triptan-related were more common in the zolmitriptan 5 mg group than in the other treatment groups (table 5). The tolerability profile in the analysis looking at adverse events up to 14 days after dosing was similar to that described above for adverse events occurring within 48 h (table 5). No patients died during the study. Only one serious adverse event was reported during the study, and that was in a patient taking placebo.

Laboratory abnormalities during the study were rare, and there were no clinically relevant differences between treatment groups. Other assessments, including the proportion of patients who exceeded predefined levels of change on laboratory parameters, vital sign measurements, electrocardiography measurements, and physical examinations, indicated no clinically meaningful differences between treatment groups.

Discussion

Our study in 1380 people with migraine confirmed that an oral 300 mg dose of the CGRP-receptor antagonist telcagepant is effective in the treatment of a moderate or severe migraine attack. This was true across a range of

	Within 48 h				Within 14 days			
	Telcagepant 150 mg (n=334)	Telcagepant 300 mg (n=352)	Zolmitriptan 5 mg (n=345)	Placebo (n=349)	Telcagepant 150 mg (n=334)	Telcagepant 300 mg (n=352)	Zolmitriptan 5 mg (n=345)	Placebo (n=349)
Any	95 (28·4%)	120 (34·1%)	174 (50·4%)	107 (30·7%)	105 (31·4%)	131 (37·2%)	175 (50·7%)	112 (32·1%)
Dry mouth	18 (5·4%)	21 (6·0%)	28 (8·1%)	13 (3·7%)	18 (5·4%)	21 (6·0%)	28 (8·1%)	13 (3·7%)
Somnolence	15 (4·5%)	18 (5·1%)	19 (5·5%)	14 (4·0%)	15 (4·5%)	19 (5·4%)	20 (5·8%)	14 (4·0%)
Dizziness	14 (4·2%)	18 (5·1%)	38 (11·0%)	20 (5·7%)	15 (4·5%)	19 (5·4%)	38 (11·0%)	20 (5·7%)
Nausea	13 (3·9%)	16 (4·5%)	20 (5·8%)	13 (3·7%)	13 (3·9%)	17 (4·8%)	20 (5·8%)	13 (3·7%)
Fatigue	14 (4·2%)	15 (4·3%)	24 (7·0%)	8 (2·3%)	14 (4·2%)	15 (4·3%)	24 (7·0%)	8 (2·3%)
Vomiting	2 (0·6%)	8 (2·3%)	4 (1·2%)	2 (0·6%)	2 (0·6%)	8 (2·3%)	4 (1·2%)	3 (0·9%)
Paraesthesia	4 (1·2%)	6 (1·7%)	18 (5·2%)	5 (1·4%)	4 (1·2%)	6 (1·7%)	18 (5·2%)	5 (1·4%)
Chest discomfort	1 (0·3%)	3 (0·9%)	10 (2·9%)	1 (0·3%)	1 (0·3%)	4 (1·1%)	10 (2·9%)	1 (0·3%)
Asthenia	0	3 (0·9%)	9 (2·6%)	3 (0·9%)	0	3 (0·9%)	9 (2·6%)	3 (0·9%)
Feeling hot	6 (1·8%)	2 (0·6%)	7 (2·0%)	1 (0·3%)	6 (1·8%)	2 (0·6%)	7 (2·0%)	1 (0·3%)
Throat tightness	0	1 (0·3%)	9 (2·6%)	0	0	1 (0·3%)	9 (2·6%)	0
Myalgia	0	0	8 (2·3%)	0	0	0	8 (2·3%)	0
Triptan-related adverse events*	7 (2·1%)	14 (4·0%)	36 (10·4%)	12 (3·4%)	7 (2·1%)	15 (4·3%)	36 (10·4%)	12 (3·4%)

Data are number (%). *Chest pain, chest tightness, asthenia, paraesthesia, dysaesthesia, hyperaesthesia.

Table 5: **Adverse events reported by 2% or more of participants in any study group**

outcome measures. On the basis of closed-testing procedure, formal statistical significance versus placebo can only be claimed for telcagepant 300 mg on the co-primary endpoints and key secondary endpoint. However, on the basis of nominal p values and inspection of the data, the 150 mg dose of telcagepant and zolmitriptan 5 mg also seemed more effective than placebo. The 300 mg dose of telcagepant was more effective than the 150 mg dose and as effective as zolmitriptan 5 mg. The efficacy of zolmitriptan in our study was similar to that observed in previous studies[2] and generally greater than telcagepant 150 mg. The apparent dose-response for telcagepant validates the dose-selection based on the previous phase II adaptive dose-ranging study.[19]

The suggestion in the previous phase II study that telcagepant might be more effective than an established triptan treatment in providing sustained duration of pain relief or pain freedom up to 24 h was not supported in our study. In an exploratory analysis, telcagepant 300 mg was more effective than zolmitriptan up to 48 h, but this finding should be treated with caution because it was only one of many exploratory analyses done without adjustment for multiplicity.

The number of patients planned for each treatment group (382) was more than the number actually studied (333 to 354), because more patients than anticipated did not treat an attack. However, this did not effect the conclusions of the study because outcomes for the five co-primary hypotheses for which power was calculated were all statistically significant.

The population studied (mostly women with a mean age of about 40 years) was largely comparable with that studied in previous migraine clinical trials. Patients were instructed to only treat a moderate or severe migraine attack, as has been the standard approach to clinical trials for triptans.[2] Recent studies have shown that triptans might be more effective when given earlier in the attack, although this is at the expense of an increased placebo response.[25,26] Therefore, the absolute response rates observed here may underestimate those seen in real-life clinical practice in which patients may treat early, although this needs to be confirmed in appropriately designed trials.

As was observed in the phase II trial (which examined doses up to 600 mg),[19] telcagepant was generally well-tolerated for the acute treatment of migraine. Most clinical adverse events occurred within 48 h of dosing. Both doses of telcagepant 150 mg and 300 mg were associated with fewer clinical adverse events than zolmitriptan, suggesting that telcagepant might offer tolerability advantages over current triptan treatments. The difference was in part due to fewer adverse events prespecified as triptan-related (eg, chest discomfort, asthenia, paraesthesia) but also a reduction in other adverse events associated with zolmitriptan, such as dry mouth, nausea, myalgia, dizziness, somnolence, and throat tightness.

One potential benefit of the new CGRP receptor antagonist class of acute migraine treatments is the absence of vasoconstriction, a liability of the triptans, which may allow for the safe administration of telcagepant in patients with migraine with cardiovascular disease. However, such patients were excluded from the present study because of the contraindication for zolmitriptan, and further studies are necessary to determine the safety of telcagepant in patients with cardiovascular disease. Additional studies are also necessary to assess the long-term efficacy and safety profile of telcagepant in patients treating more than one migraine attack.

Contributors

TWH participated in planning the study, collecting the data, supervising the analyses, and interpreting the results. MDF participated in planning the study, data collection, and interpreting the results. DWD participated in interpreting the results. VG participated in planning the study, and interpreting the results. JK participated in planning the study, doing the analyses, and interpreting the results. XF participated in planning the study, doing the analyses, and interpreting the results. HL participated in planning the study and data collection. SF participated in planning the study and data collection. CA participated in planning the study, doing the analyses, and interpreting the results. CL participated in interpreting the results. HK participated in data collection and interpreting the results. PKW participated in data collection and interpreting the results. CL, TWH, and JK wrote the first draft of the Article. All authors were involved in planning the Article, critical review and editing of the first draft, and subsequent revisions to the paper.

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Conflict of interest statement

TWH, VG, JK, XF, HL, SF, CA, and CL are employees of Merck and own stock or stock options in Merck. MDF has, in the past 3 years, received grants and consultancy or industry support from Almirall, Coherex, Colucid, Eisai, GlaxoSmithKline, Linde, MAP, Medtronic, Menarini, Merck, Minster, Pfizer, and St Jude, and independent support from NWO, NIH, European Community FP6, Biomed EC, and the Dutch Heart Foundation. DWD has received honoraria from and has consulting agreements with Allergan, Pfizer, Merck, Endo, OrthoMcNeil, Coherex, MAP, Neuralieve, Addex, Solvay, Eli Lilly and has research grants from AstraZeneca, Medtronic, St Jude, and Advanced Neurostimulation Systems. HK has received research funding from Merck. PW has received grant, consultancy, or industry support from Allergan, Forest, GlaxoSmithKline, Merck, Minster, OrthoMcneil, Pfizer, and Wyeth.

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CGRP-receptor antagonism in migraine treatment

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In *The Lancet* today, Tony Ho and colleagues present the first phase III trial of a novel oral calcitonin-gene-related peptide (CGRP) receptor antagonist, telcagepant, which they tested against one of the currently most effective triptans, zolmitriptan, and against placebo.[1] The drug acts through a novel antimigraine mechanism by blocking the action of CGRP on the CGRP-receptor complex. In the study telcagepant had an antimigraine effect that was not significantly different from that of zolmitriptan but with fewer side-effects. Many scientific questions still remain to be solved but the results open a new option in migraine treatment.

The field of CGRP research began with Geoff Rosenfeld and colleagues, who found that the calcitonin gene encodes CGRP in neural tissue and that the peptide is expressed in both the central and peripheral nervous systems.[2] Our group identified CGRP-containing nerve fibres in the walls of intracranial vessels, as well as CGRP in the cell bodies of neurons of the trigeminal ganglion that coexpressed substance P. Furthermore, surgical denervation of the trigeminal nerve specifically removed the CGRP fibres in intracranial arteries.[3] Drug studies showed that CGRP acts on smooth-muscle cells to cause potent dilation, while substance P and acetylcholine require an intact endothelium to produce relaxation of cerebral arteries.[4] Additionally, the relaxant response to CGRP occurs via activation of adenylate cyclase and the production of cAMP.[4] In vivo, CGRP was the most potent arteriolar dilator at that time but, amazingly, had little effect on cerebral veins.

We were intrigued with the role of CGRP-containing sensory nerve fibres in the cerebral circulation and therefore did unilateral denervation experiments in cats; to our disappointment, the denervation did not change the basic mechanisms for regulation of brain circulation. Thus autoregulation, blood-gas responses, flow-metabolism coupling, or resting cerebral blood flow were not altered.[4] However, the return to baseline after the contractile response elicited by perivascular noradrenaline was significantly delayed on the denervated side of the brain compared with the contralateral side. These data indicate that the CGRP-containing sensory nerve fibres act to counter vasoconstrictor influences.[5-7] Subsequent studies verified that this response, the trigeminovascular reflex, could be elicited by other vasoconstrictors.[7]

In a collaboration between our university and Peter Goadsby in Sydney, we designed experiments to test the hypothesis that CGRP is a key molecule in primary headaches. We showed that treatment of trigeminal neuralgia with thermocoagulation correlated with strong release of both CGRP and substance P in the jugular venous blood of patients. These findings were then followed by the demonstration that CGRP is released during migraine[8,9] and cluster-headache attacks.[10] Despite these data, our idea that CGRP is a key mediator in primary headaches received little support for more than a decade. At the time, researchers were mainly interested in the concept of neurogenic inflammation in the dura mater and focused on potential mediators, such as substance P. Several compounds were tested because of their ability to inhibit neurogenic inflammation in animal models, but they all failed in human trials. The CGRP hypothesis was finally tested when the specific CGRP-receptor antagonist olcegepant was shown to have similar effectiveness in reducing acute migraine pain to that of triptans. Olcegepant also had a longer duration

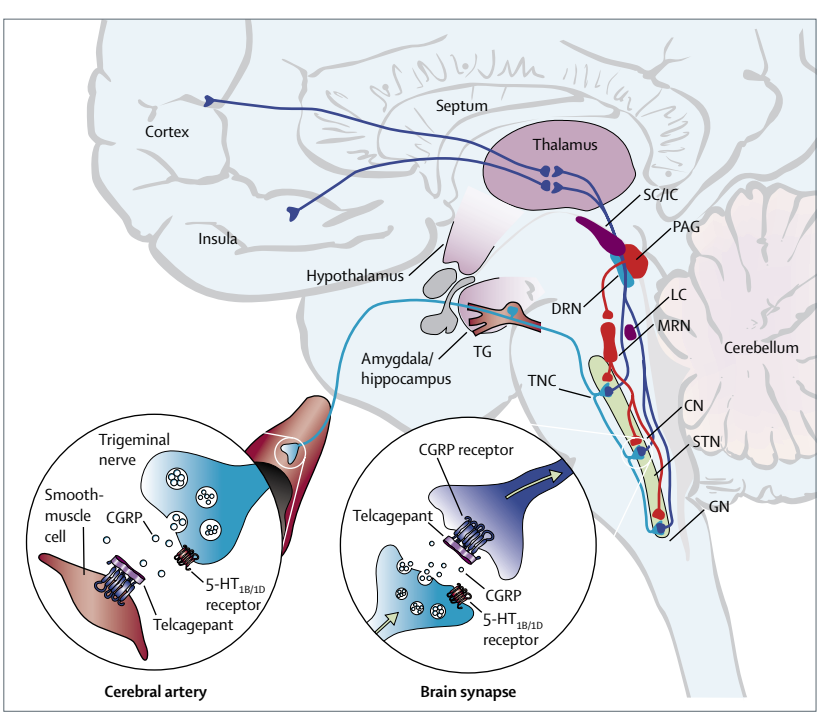

Figure: **Brain areas expressing CGRP receptor that are possible sites of action of telcagepant in migraine treatment**
SC/IC=superior colliculus and inferior colliculus. PAG=periaqueductal grey. DRN=dorsal raphe nucleus. LC=locus ceruleus nucleus. MRN=median raphe nucleus. TNC=trigeminal nucleus caudalis. CN=cochlear nucleus. STN=solitary tract nucleus. GN=gracile nucleus. 5-HT=serotonin. Left-hand insert shows blockade of CGRP receptors on cerebral artery. Right-hand insert shows blockade of CGRP receptors at central synapses.

of action and fewer side-effects.[11] A phase IIb study of the first orally available CGRP-receptor antagonist, telcagepant, confirmed these data.[12]

Ho and colleagues' results show equally good efficacy at all timepoints for both telcagepant and zolmitriptan. However, telcagepant is associated with a lower incidence of side-effects than the triptan. This result marks a new era in migraine therapy. However, the remaining issue is to understand the site of action of the CGRP-receptor antagonists. There are three potential targets: the intracranial blood vessels, parts of the trigeminal nerve, either at the peripheral or central ends, or the CNS, in several areas that include the trigeminal nucleus caudalis, periaqueductal grey matter, nucleus solitarius, amygdala, and the colliculi (figure).[13,14] Ho's data are intriguing because the clinical dose is high in view of the potency of telcagepant, which suggests a central antimigraine action within the CNS. While this new drug will be of value to clinicians, scientists will battle with these questions. Despite the use of triptans for two decades, their site of antimigraine effect remains debated. As for CGRP-receptor antagonists, the question will be whether inhibition of CGRP released peripherally from sensory nerves is sufficient for their antimigraine action, or is inhibition of CGRP acting centrally in brainstem trigeminal pain-relay nuclei of the brainstem or other nuclei also a key contributor to their clinical effectiveness?

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I declare that I have no conflict of interest.

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