CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20768

MEDICAL REVIEW(S)

Review And Evaluation Of Clinical Data

NDA:	**20-768**
Sponsor:	**Zeneca**
Drug:	**Zolmitriptan**
Indication:	**Migraines**
Material Submitted:	**NDA**
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Background:

Zeneca submitted NDA 20-768 for Zolmitriptan, a 5 HT1D receptor agonist, for the indication of acute treatment of migraine headaches. In this document, I have reviewed the evidence presented to support the efficacy of the drug in the acute treatment of migraine headaches. Dr. Liu has provided a statistical consult for the efficacy data and Dr. Oliva has reviewed the evidence supporting the safety of the drug in patients with migraine headache.

This review is divided into four parts. The first part includes an overview of the efficacy portion of the NDA. The second and third part include a summary of the sponsor's conclusions and my comments, respectively. In the final part, I have provided specific details and analyses for each of the efficacy studies.

Part One: Overview of efficacy studies

Overview:

The sponsor has conducted a total of 8 clinical trials evaluating the drug for the acute treatment of migraine headaches. Four of these studies, 006, 008, 017 and 042, were presented as adequate and well controlled, pivotal studies providing evidence for efficacy of the drug for the acute treatment of migraines. The other four studies were designated by the sponsor as supportive trials. Three of these studies, 002, 007 and 015 were uncontrolled studies. The fourth study, 018, compared zolmitriptan, sumatriptan and placebo for the treatment of migraine. Another trial, 026, was conducted for the prevention of migraines. The studies are summarized below and in table 8.1 from the sponsor's NDA.

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Table 8.1. Categorization of Zolmitriptan (311C90) Efficacy Studies

Study Category	Study Characteristics	Primary Endpoint	Study Number	311C90 Doses Used (mg)	Number of Unique Patients
PATIENT CONTROLLED STUDIES FOR TREATMENT OF MIGRAINE					
Adequate and Well-Controlled	inpatient, optional 2nd dose, placebo-controlled efficacy single attack, dose range finding	headache response at 2 hrs	006	1, 5, 25	84
	outpatient, single dose, placebo-controlled efficacy single attack, dose range finding	headache response at 2 hrs	008	5, 10, 15, 20	951
	outpatient, optional 2nd dose, placebo-controlled efficacy single attack, dose range finding	headache response at 2 hrs	017	1, 2.5, 5, 10	1144
	outpatient, single dose, placebo-controlled efficacy single attack	headache response at 2 hrs	042	2.5	301
	TOTAL ADEQUATE AND WELL-CONTROLLED				2480
Active-Controlled	outpatient, single dose, active-controlled efficacy, single attack	"complete response"	018	5, S-100*	1058
	TOTAL ACTIVE-CONTROLLED				1058
Non-controlled	outpatient, optional 2nd dose, open-label, long-term efficacy, multiple attacks	headache response at 2 hrs	015	5	1128
	inpatient, single dose, open-label, efficacy PK patients	headache response at 2 hours	002	25	18
			007	10	20
	TOTAL NON-CONTROLLED				150
TOTAL STUDIES FOR TREATMENT OF MIGRAINE					3688
PATIENT CONTROLLED STUDIES FOR TREATMENT OF MIGRAINE HEADACHE					
Controlled	outpatient, optional 2nd dose, placebo-controlled efficacy single attack, dose range finding	prevention of headache	026	20	30
TOTAL STUDIES FOR PREVENTION OF MIGRAINE					30
TOTAL OF ALL 311C90 EFFICACY STUDIES					3718

* S-100 = sumatriptan 100 mg

Summary of the pivotal and supportive clinical trials:

Study 002: The evaluation of the drug was initiated in June of 1992 with a PK study in healthy volunteers. Oral doses of 1 to 50 mg were evaluated. The first study in patients, study 002, was initiated in September of 1992 and evaluated the

PK and safety of the 25 mg dose.

Study 006: The next study in patients, study 006, was initiated in March of 1993. This phase 2 trial was the first placebo controlled study to evaluate efficacy. 84 patients were randomized to doses of 0, 1, 5 and 25 mg. Evaluating the response rate, defined as the proportion of patients with headache pain going from moderate or severe to mild or no pain, at 2 hours, the sponsor found all active doses to have statistically significant higher rates when compared to placebo, except for the 1 mg dose. There was no difference between the 5 and 25 mg dose group. See the following tables for a summary of the results.

Study 006: Percentage of patients with headache relief * P value < 0.05				
	Placebo (N=20)	1 mg (N=22)	5 mg (N=21)	25 mg (N=21)
1 hour	15	9	24	43
2 hours	15	27	62*	81*

Study 006: Summary of secondary outcome measures (using the sponsor defined protocol preferred data set)				
	Placebo (N=20)	1 mg (N=22)	5 mg (N=21)	25 mg (N=21)
% of patients headache free rate at 2 hours	5%	9%	14%	38%
% of patients with nausea at 2 hours	35%	59%	24%	10%
% of patients with photophobia at 2 hours	65%	59%	43%	29%
% of patients using a rescue medication	20%	23%	14%	10%

Study 008: In May of 1993, the sponsor conducted the second open label study, 007, to evaluate the safety and PK of 10 mg doses. This was followed by the second, placebo controlled efficacy study, 008. This was a large, multinational study initiated in September of 1993. 951 patients were randomized to 0, 5, 10, 15 and 20 mg in a 1:2:2:2:2 ratio, respectively. The sponsor reported a statistically significant higher response rate at 2 hours in all dose groups compared to placebo without a difference between groups. See the following two tables for a summary of the results.

Study 008: Percentage of patients with headache relief *P value < 0.05					
Hours after dosing	Placebo (N=99)	5 mg (N=213)	10 mg (N=213)	15 mg (N=215)	20 mg (N=209)
1 hour	16%	44%	40%	42%	50%
2 hours	21%	61%*	67%*	67%*	74%*

Study 008: Summary of secondary outcome measures (using the sponsor defined protocol preferred data set)					
	Placebo (N=88)	5 mg (N=179)	10 mg (N=191)	15 mg (N=194)	20 mg (N=188)
% of patients headache free rate at 2 hours	1%	39%	39%	43%	47%
% of patients without recurrent headache or rescue/second dose	7%	49%	51%	55%	55%
% of patients with nausea at 2 hours	34%	27%	31%	32%	29%
% of patients with photophobia at 2 hours	59%	32%	35%	37%	27%
% of patients with phonophobia at 2 hours	55%	31%	30%	34%	28%
% of patients using a rescue medication	81%	53%	50%	42%	41%
Time (hours) to use of rescue medication	3.7	7.4	9.8	8.2	8.9
Number of patients with recurrence/ Number of patients with headache relief at 2 hours (%)	11/17 (65%)	32/118 (26%)	39/136 (28%)	28/134 (21%)	42/145 (29%)
Mean time (hours) to recurrence	8	14.6	15.4	13.0	15.5

Study 017: In November of 1994, the sponsor launched study 017, a large efficacy trial conducted in the US. 1144 patients were randomized to doses of 0, 1, 2.5, 5 and 10 mg in a ratio of 1:1:2:2:2, respectively. In this study, the sponsor reported all doses to have statistically significant higher response rates at 2 hours when compared to placebo. The response rate for patients treated with 2.5 mg was significantly higher when compared to patients receiving 1 mg. There was no difference between patients receiving doses of 2.5, 5 and 10 mg. Noting that the tolerability, as determined from the adverse event reported, was similar between the 1 and 2.5 mg group and increased as the dose increased from 2.5 mg, the

sponsor chose the 2.5 mg dose as the optimal dose. In this study, patients who did not respond to the initial dose, received a second dose of either placebo or active drug in a randomized fashion. The response rate of the second dose was numerically but not statistically higher if the patient received active drug compared to placebo. See the following tables for a summary of the results.

Study 17: Percentage of patients with headache response					
Hours after dosing	Placebo (N=139)	1 mg (N=140)	2.5 mg (N=297)	5 mg (N=279)	10 mg (N=283)
0.5 hours	14%	14%	16%	20%	20%
1 hour	24%	33%	43%*	44%*	50%*
2 hours	32%	50%*	63%*#	65%*#	65%*#
4 hours [a]	28%	52%*	70%*#	69%*#	70%*#

* p value < 0.05 when compared to placebo
# p value < 0.05 when compared to 1 mg
[a] 78 patients took escape medication prior to the 4 hour time point (17 on placebo, 10 on 1 mg, 18 on 2.5 mg, 20 on 5 mg, 13 on 10 mg)

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Study 17: Summary of secondary outcome measures					
	Placebo (N=140)	1.0 mg (N=141)	2.5 mg (N=298)	5 mg (N=280)	10 mg (N=285)
% of patients headache free rate at 4 hours	9%	30%	41%	46%	53%
% of patients without recurrent headache or rescue/second dose	14%	27%	33%*	39%*	47%*
% of patients with nausea at 240 minutes	40%	24%	20%	20%	17%
% of patients with vomiting at 240 minutes	9%	3%	4%	2%	1%
% of patients with photophobia at 240 minutes	65%	45%	32%	25%	25%
% of patients with phonophobia at 240 minutes	57%	35%	24%	22%	24%
% of patients using a rescue medication	69%	46%	44%	41%	36%
Time (hours) to use of rescue medication	6.0	7.4	9.1	9.8	10.6
% of patients using a second dose of study treatment	52%	52%	47%	43%	33%
Time (hours) to use of second dose	5.5	6.7	9.4	9.2	9.4
% of patients using rescue medication and/or a second dose	84%	71%	64%	59%	49%
Time (hours) to use of rescue medication and/or second dose	2.8	3.9	5.5	5.7	6.6
Number of patients with recurrence/ Number of patients with headache relief at 4 hours (%)	17/39 (44%)	38/73 (52%)	102/209 (49%)	84/193 (44%)	81/200 (40%)
Mean time (hours) to recurrence	14.7	14.3	14.4	13.3	15.2
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (mod or severe) (%)	13/32 (41%)	18/48 (38%)	31/102 (30%)	21/82 (26%)	29/72 (40%)

*P value < 0.05

Study 042: In December of 1995, the sponsor initiated study 042, a large efficacy, to confirm the efficacy of the 2.5 mg dose. A total of 301 patients were treated with 0 or 2.5 mg in a 1:2 ratio, respectively. The sponsor reported that the response rate at 2 hours was significantly higher in the 2.5 mg dose group when compared to the placebo group, thus establishing the efficacy of 2.5 mg of zolmitriptan in the acute treatment of migraine headaches.

Study 42: Percent of patients with relief (no or mild pain) following the initial treatment *p< 0.05		
Hours post dose	Placebo (relief/N)	2.5 mg (relief/N)
1	26% (26/100)	33% (66/198)
2	35% (35/100)	60%* (119/197)
4	35% (32/94)	68%* (126/184)

Study 42: Summary of secondary outcome measures		
	Placebo (N=101)	2.5 mg (N=200)
% of all patients with headache free rate at 4 hours	12%	34%
% of all patients with relief at 4 hours without recurrent headache or rescue	14%	34%
% of patients with nausea at 240 minutes	41%	18%
% of patients with photophobia at 240 minutes	61%	31%
% of patients with phonophobia at 240 minutes	40%	26%
% of patients using a rescue medication	65%	40%
Time (hours) to use of rescue medication	9.7	10.4
Number of patients with recurrence/ Number of patients with headache relief at 4 hours (%)	16/33 (48%)	36/127 (28%)
Mean time (hours) to recurrence	9.1	13.5
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (mod or severe) (%)	1/33 (3%)	4/127 (3%)

Study 018: Two additional studies evaluating the acute treatment of migraine headaches were performed. In December of 1994, the sponsor conducted a large study, 018, comparing a 5 mg dose of the drug with 100 mg of sumatriptan and placebo. Over 1000 patients were enrolled with only 56 receiving placebo. At 2 hours, both drugs had a statistically significant higher response rate when compared to placebo. There was no statistically significant difference between the active treatments. The results are summarized in the following two tables.

Study 18: Headache relief rates (*comparison with placebo p value < 0.05)			
Time post dose	0 mg N=55	5 mg N=495	Sumatriptan N=503
60 minutes	20	34	35*
120 minutes	44	59*	62*
240 minutes	40	73*	77*

Study 18: secondary outcome measures	Placebo (N=55)	5 mg (N=495)	Sumatriptan (N=503)

Study 18: secondary outcome measures	Placebo (N=55)	5 mg (N=495)	Sumatriptan (N=503)
Headache free rate at 4 hours	13	29	30
% of patients with nausea at 120 minutes	40	31	33
% of patients with photophobia at 120 minutes	51	34	32
% of patients with phonophobia at 120 minutes	49	37	34
% of patients using a rescue medication	56	38	36
Time (hours) to use of rescue medication	5.1	9.8	8.4
Number of patients with recurrence/ Number of patients with headache relief at 2 hours (%)	8/24 (33%)	73/28 (26%)	74/301 (25%)

Study 015: Study 015, started in December of 1994, was an open label, long term safety study where 2058 patients treated migraines headaches with 5 mg doses over the course of a year. Patients were allowed to take a second dose of 5 mg. The 2 hour response rate for the patients treating moderate to severe headaches was similar over the duration of the study. 2/3 of the patients who treated ≥ 5 headaches over the year had a response by 2 hours for ≥ 80% of headaches that they treated.

Study 026: One study, 026, was conducted to evaluate the acute prevention of migraine headaches. In this study, started in September of 1994, 30 patients were randomized in a two period cross over study. Patients received doses of 0 or 20 mg given during a migraine aura. All 22 patients who treated an aura with placebo went on to have a migraine headache. Of the 23 patients receiving 20 mg

19 (83%) went on to have a migraines headache. No further studies were included for this indication.

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Part Two: Sponsor's conclusions:

The following is from the Integrated Summary of Efficacy (page 3 to 5):

Data from the four adequate and well–controlled studies substantiate the following claims:

- Efficacy has been well established in at least two adequate and well–controlled studies for 2.5, 5, and 10 mg doses of zolmitriptan.
- Zolmitriptan is efficacious in reducing the pain symptoms of migraine headache and the effects of associated symptoms (photophobia, phonophobia, and nausea) in patients with migraine.
- The efficacy of zolmitriptan is not affected by the presence or absence of aura or by age, gender, weight, menstrual cycle, or the duration of migraine attack.
- The recommended initial dose is 2.5 mg.
- In Study 017, where a direct comparison between 2.5 mg and 5 mg was available, there was no statistically significant difference in headache response at two hours between the two doses. However there was a trend in certain secondary efficacy endpoints (e.g., headache pain free, use of rescue medication, complete response, and nausea) for 5 mg to show added benefit over 2.5 mg, though these differences were not tested statistically.
- Significant headache response with zolmitriptan doses of 2.5 mg and above was observed by 1 hour post dose, this increased over time (at 2 and 4 hour assessments).
- Doses lower than 2.5 mg (i.e., 1 mg) provided inadequate migraine relief. The 1 mg dose was significantly less effective than both the 2.5 and 5 mg doses of zolmitriptan with regard to headache relief at 2 hours, and was not consistently distinguishable from placebo for the relief of migraine headache symptoms.
- A second dose of zolmitriptan has been shown to provide significant benefits in cases where there was an incomplete response to the first dose.

In addition to the information provided by the four adequate and well–controlled studies, the supportive studies (one active–controlled, Study 018; and 3 non–controlled, Studies 002, 007, and 015) contributed the following information:

- Zolmitriptan effectiveness does not diminish with continued use over time (and within patients), as evidenced by Study 015 in which a total of 31579 migraine attacks were treated by 2058 patients.
- In Study 015, for nearly 70% of patients who treated at least 5 attacks, the headache response at 2 hours was consistently 80% to 100%.

- In Study 015, 90% of migraine headaches treated with a second 5 mg dose of zolmitriptan responded to treatment by 2 hours; 65% of the patients treating a moderate or severe headache with a second 5 mg dose of zolmitriptan reported being pain free post–treatment.
- In Study 015, zolmitriptan provided headache relief to patients treating a mild headache as well as patients who treated moderate or severe headaches.
- Patients received considerable relief as early as 1 hour post–dose as evidenced by data from Study 015 where the median time to meaningful migraine relief was 1 hour.
- Zolmitriptan 5 mg provided comparable relief to sumatriptan 100 mg in a head–to–head trial.

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Part three: Reviewer's comments

Background:

In my discussion of the efficacy findings, I am going to concentrate on the aspects that relate to the clinical trials section of labeling. Zolmitriptan is one in a series of 5 HT1 agonists that are being evaluated for the treatment of migraines. With the recent approval of Imitrex Nasal Spray, the division has worked on certain aspects of labeling, both safety and efficacy that can be consistent between drugs in this class and I will refer to these areas in my discussion.

Pivotal studies:

The sponsor has provided 5 studies (6, 8, 17, 18, and 42) that are adequate by design to provide evidence for efficacy of the drug in the acute treatment of migraines. Three studies, 8, 17 and 42, had similar designs. In study 6, patients were treated in a clinic setting whereas in studies 8, 17 and 42, patients treated their headache on their own. This design difference may lead to differences in the types of headaches treated and the timing of treatment which may result in differences in headache response. Study 18 was a comparison trial with sumatriptan and excluded patients who had experience with sumatriptan. This was not a part of the other studies and may results in a different patient population being enrolled. All studies are capable by design for demonstrating evidence for efficacy but I have chosen not be combine the results from studies 6 and 18 with studies 8, 17 and 42.

Not all of the studies evaluated the same doses. Two studies evaluated a single 1 mg dose, two studies evaluated the 2.5 mg dose, four studies evaluated dose of 5 mg and three studies looked at doses > 5 mg. One study evaluated the efficacy of a second dose of 1, 2.5 and 5 mg.

All studies allowed either a second dose and/or rescue treatment after an initial observation period of 2 to 4 hours. Headache pain severity, secondary symptoms and use and/or time to rescue were recorded.

All studies enrolled adults under the age of 65. In study 17, 14 patients out of the 1144 enrolled were between the ages of 12 and 17.

Efficacy: The sponsor has demonstrated in more than one adequate and well

controlled study that zolmitriptan is effective for the acute treatment of migraine headaches. The sponsor's prospectively defined measure of efficacy was the response rates 2 hours following treatment with response defined as a reduction in headache pain severity from moderate or severe to mild or no pain. This outcome measure is the same used in most recent migraine studies. In each study, there was a statistically significant increase in headache response rates in patients treated with the drug compared to those patients treated with placebo. The finding were consistent across studies.

Dose effect: Using the efficacy criteria of headache response at 2 or 4 hours, there were statistically significant differences from placebo for all doses tested (range 1 mg to 25 mg). Only in study 6 was there a non statistically significant difference between the active treatment and placebo. This was in the comparison of the 22 patients in the 1 mg dose group and 20 patients in the placebo dose group. The 1 mg group was numerically better than the placebo group but the difference did not reach statistical significance. This is in contrast to the results in study 17 were the comparison between 140 patients in the placebo and 1 mg groups was statistically significant.

There is evidence for a greater effect with higher doses. In study 17, there was a statistically significant difference between the response rates in the 1 mg dose and the higher doses including 2.5 mg. In no other study was there a statistically significant difference between treatment groups. In regards to other outcome measures, such as incidence of associated symptoms and use of rescue, the 1 mg group numerically falls in between placebo and the higher doses. The higher doses are similar in regards to the secondary outcome measures.

The drug is effective and the results from the studies provide evidence for efficacy for doses of 1 mg and above and as well as evidence that dose $\geq$ 2.5 mg are more effective than doses of 1 mg. There is no evidence that doses of $\geq$ 5 mg are any more effective than 2.5 mg.

Onset of effect: Response rates were evaluated as early as 30 minutes following treatment. In study 17, a statistically significant difference in response rates were seen as early as 1 hour for doses $\geq$ 2.5 mg and 2 hours for the 1 mg dose. Time to effect was not directly addressed by the studies. To illustrate the time to response, we have used a Kaplan Meier plot of the estimated probability of achieving a headache response over the 4 hours following treatment.

Duration of effect for the treatment of a single headache: From

experience with sumatriptan, an acute treatment for a migraine headache may not lead to complete resolution of the headache. Patients who have mild or no pain at 2 or 4 hours may have recurrent pain and/or require additional treatments. We have used a Kaplan Meier plot of the estimated probability of the using additional treatments for migraine over the 24 hour period following treatment to illustrate the the duration of effect.

Efficacy of the second dose: The efficacy of the second dose was only assessed in study 017. The design allowed patients to be treated with a second dose for persistent headaches as well as recurrent headaches. Patients were allowed to take rescue medication instead of a second dose. For patients failing to respond to the initial dose of 2.5 mg, the response rate 2 hours following the second dose of 2.5 mg was higher than patients who were randomized to placebo for the second dose though the difference did not reach statistical significance. When the response rates for all doses, including placebo, were combined, the difference was associated with a nominal p value of < 0.05. The failure to detect a difference with the 2.5 mg dose may be a result of a number of factors including a lack of power, continued effect of the initial dose, etc.

At this time, the results of the study does not provide sufficient evidence to support the claim of efficacy of a second dose of 2.5 mg.

Associated migraine symptoms: Though not a primary outcome measure, the studies show a consistent reduction in the incidence in the secondary outcome measures of nausea, photophobia and phonophobia in patients treated with the active treatment compared to those treated with placebo.

Long term benefit: The ability of zolmitriptan to effectively treat migraine headaches repeatedly over time was not evaluated in a controlled clinical trial. Because of the variability of response and potential for placebo effect, conclusions drawn from uncontrolled clinical trials may not be valid. In study 015, the sponsor evaluated the long term safety of the drug in an open label study. Headache response was determined after each headache treatment. While the findings in this study suggest that the benefit of the drug does not dissipates over time, it has limited use in describing efficacy of the drug.

Comparison to sumatriptan: The study comparing the effects of sumatriptan and zolmitriptan was not adequate by design to demonstrate a difference between the two treatments. The dose used in this trial did not cover the entire range of effective doses for either drug. While the results showed a significant difference

for both dose groups compared to placebo, it failed to show a significant difference between the treatments.

Subgroup analyses: There were insufficient numbers of patients in each group to determine the effect of race or age < 18 on the efficacy results. The efficacy of did not appear to be affected by the presence or absence of aura or by age, gender, weight, menstrual cycle, or the duration of migraine attack.

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Part Four: Review of individual studies:

In this part, I will discuss the pivotal studies, 006, 008, 017 and 042 and the supportive studies

Protocol overview for the pivotal studies: All of these studies were randomized, placebo controlled, parallel, double blind studies that evaluated the drug during a single attack. The selection criteria were similar in that patients enrolled in these studies had 1 to 6 migraine headaches per month, with or without aura as defined by the IHC criteria. The patients were otherwise healthy and specifically had no history of heart disease, did not have high BP, lab or ECG abnormality. In study 017 and 042, patients age 12 to 65 were enrolled. In studies 006 and 008, patients ages 18 to 65 were enrolled. In all studies, headache response rates (moderate to severe pain to mild or no pain) at 2 hours was the primary outcome measure.

Methods used for analyses: For the analyses of these studies, I have used the following definitions:

Study treatment is a dose of either placebo or active drug.

Headache severity is graded by the patient on a 4 point scale with 3=severe pain, 2=moderate pain, 1=mild pain and 0=no pain.

Efficacy data set includes all patients in the study who received at least one dose of study treatment and had a baseline headache severity of moderate or severe pain.

Rescue is medication, other than the study treatment, taken for a treated migraine. Rescue includes analgesics, anti emetics, sedatives, etc.

Headache response, for the initial dose, is a change in the baseline headache severity from moderate or severe pain to mild or no pain at a given time point without intervening use of rescue or a second dose of study treatment. If there was no data available for the time of assessment, then I used data from the last available observation.

A **responder** is a patient who has a change in the baseline headache severity from moderate or severe pain to mild or no pain at a given time point without intervening use of rescue or a second dose of study treatment.

A **responder to a second dose** is a patient whose headache severity goes from severe or moderate pain just prior to the second dose to mild or no pain at a given time point following the second dose of study treatment.

A **non responder** is a patient who does not experience headache response at a given time point. In these patients, headache severity is moderate or severe at a given time point following the initial dose of study treatment from a baseline of severe or moderate pain. If there was no data available for the time of assessment, then data from the last observation was used. If a patient took rescue or a second dose of study treatment prior to the determination of the headache severity at the given time point, the patient was also considered a non responder for the initial dose of study treatment. Likewise, if a patient took rescue following a second dose of study treatment prior to determination of headache severity at a given time point, the patient was a non responder for the second dose.

Headache response rates were calculated by dividing the number of responders at a given time point by the total number of patients in the efficacy data set x 100.

Headache recurrence is when a responder has a return of moderate or severe headache pain or receives rescue or a second dose of study treatment within 24 hours of receiving the initial dose of study treatment.

Time to recurrence is the time of the return of moderate to severe headache pain, use of rescue or a second dose of study treatment which ever comes first.

Maintenance of headache response is headache response

obtained at a specified time point without headache recurrence, need for rescue or a second dose within 24 hours of the initial study treatment.

Following a preliminary review of the sponsor's analyses, it appeared that the outcome of the patients treated with doses of ≥ 2.5 mg were indistinguishable from each other. The sponsor has chosen the 2.5 mg dose as the effective dose. I have concentrated my review on comparisons of the placebo, 1 and 2.5 mg groups.

I used the efficacy data set (see definition above) in my analyses unless otherwise specified.

To gain information on the duration of the effect of the drug, I have included five comparisons: (1) headache recurrence for patients with a headache response at 4 hours post the initial dose. (2) The mean time to recurrence (including patients taking a second dose or rescue). (3) Maintenance of headache response. (4) Frequency of the use of a second dose or rescue treatment. (5) Time to use of a second dose or rescue.

If use of rescue and use of second dose was not randomized, comparisons between groups for outcome measures obtained after using a second dose or using rescue may not be valid and I did not analyze them.

To evaluate the possibility of a rebound headache. I compared the frequency and severity of the recurrent headaches.

Since the efficacy of the drug for the treatment of migraines was determined by the primary efficacy measure, headache pain, I did rely on related symptoms of migraines such as the absence of nausea, the absence of vomiting, absence of disability measures, time to meaningful relief, percentage of patients with no pain, etc, as supportive measures only. Since the sponsor has included some of these measures in the labeling, I have assessed them.

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Study 17:

Protocol: The sponsor did not provide a detailed analysis plan with the original protocol.

Design: This was a multicenter, double blind, placebo controlled, parallel, outpatient study evaluating the efficacy of an initial dose of 1, 2.5, 5 and 10 mg as well as a second dose of drug. At baseline, patients were randomized to the initial dose group as well as the second dose group. The randomization for the initial dose was not balanced while the randomization for the second dose was balanced between the original study treatment or placebo. The following table outlines the randomization groups.

Table 1. Allocation of Treatments

Treatment Group	Tablet 1	Tablet 2	N*
I	placebo	placebo	150
II	1 mg	placebo	75
III	1 mg	1 mg	75
IV	2.5 mg	placebo	150
V	2.5 mg	2.5 mg	150
VI	5 mg	placebo	150
VII	5 mg	5 mg	150
VIII	10 mg	placebo	150
IX	10 mg	10 mg	150

* Sample size is approximate; based on enrollment of 1200 patients

Patients who had a headache between 4 and 24 hours (either a recurrence of headache or persistent headache) and had not taken rescue medication are eligible to receive a second study treatment. Patients are allowed to take rescue medication 4 hours after the initial dose or two hours after the second dose.

Selection: Patients age 12 to 65 who, on average, had 1 to 6 migraines per month, were to be enrolled. The patients were otherwise healthy. Patients were to treat headaches with moderate to severe pain with a duration of < 12 hours. The patients were supposed to be migraine free for 48 hours prior to treating the headache. The patient must have been free of an aura for at least 10 minutes and the aura must

have lasted less than 40 minutes.

Schedule: Efficacy assessments were obtained at 0, 0.5, 1, 2, 4 and 24 hours following the initial dose and 0, 2 and 24 hours following the second dose, if taken.

Sample: Assuming response rates for placebo and active drug to be 25 and 60%, respectively, 90% power and alpha level of 0.05, a minimal of 34 and 68 patients were needed in the placebo and active group, respectively. To provide additional information about safety of patients taking one or two doses, 150 and 300 patients were to be enrolled.

Outcome: Primary: Headache response defined as a reduction in headache pain from moderate or severe to mild or no pain at 2 hours following the initial dose.

Secondary:

Headache response at 0.5, 1 and 4 hours post treatment

Headache recurrence of moderate or severe pain for patients initially responding a 2 hours.

Headache recurrence of moderate or severe pain for those initially responding at 4 hours.

Time to recurrence

Prevalence of migraine symptoms at 0.5, 1, 2 and 4 hours post treatment

Meaningful migraine relief

Persistent headache is defined as a headache that is mild, moderate or severe at 4 hours post tablet 1 and is not a recurrent headache.

use of escape medication

Time to first use of escape medication

complete response defined as response at 2 hours without recurrence of moderate or severe pain within 24 hours

Headache characterization: 0=no pain, 1=mild pain, 2= moderate pain and 3=severe pain.

Time to meaningful relief as determined by the patient was recorded if it occurred within the first 4 hours of the first dose and within the first 2 hours of the second dose.

Health economics: patients recorded if they took off time from work as a result of the migraine and how much time was missed from work and when normal activities were restarted.

Analysis: Data sets include an all treated population consisting of all patients known to have taken any study medication and a protocol preferred population consisting of those who reasonably adhered to all protocol requirements.

Subgroups: sex. Age, presence of aura, initial headache severity, weight, duration of headache at treatment and menstruation.

For the second dose all the dose groups found to be effective after taking the first dose will be combined and compared with placebo.

Results:

Disposition: The study was conducted from 11/30/94 to 7/26/95. A total of 1258 patients were randomized. The disposition of patients is summarized in the following table.

Disposition of patients and protocol violations					
	Placebo	1 mg	2.5 mg	5 mg	10 mg
Number of patients randomized	154	158	317	313	316
Number of patients who did not take any study treatment	14	17	19	33	31
Number of patients with mild headache at baseline	0	0	0	0	2
Number of patients without baseline assessment	1	1	1	1	0
Total patients in efficacy data set	139	140	297	279	283
Patients who took 2nd dose	74	75	144	123	96
Took escape or 2nd tablet < 2 hrs after tablet 1	17	10	20	20	16

Demographics and baseline characteristics: The sponsor did not find any significant differences between groups in the demographic profile or baseline characteristics including the 114 patients excluded from the efficacy data set. The mean age was 41.4 with a range of 12 to 65. 88% were female and 94% were white. 65% of the patients had migraines without auras. The average number of migraines per month was 3.2. 49% of the patients were current users of subcutaneous sumatriptan with 76% reporting a good response. 1% of patients were current users of oral sumatriptan. 76% of the patients had a moderate headache at baseline with a mean duration of 3.6 hours between onset and treatment. 50% had nausea, 82% had photophobia and 73% had phonophobia.

Primary efficacy measure: The percentage of patients with headache relief is summarized in the following table. By one hour, the response rate for doses ≥ 2.5 mg was significantly better than placebo. By 2 hours, the 1 mg dose was significantly better than placebo. Also by 2 hours, the doses ≥ 2.5 mg was significantly better than the 1 mg dose. There was no statistical difference between doses groups ≥ 2.5 mg. 78 patients took rescue prior to 4 hours. All of the rescue was taken between 2 and 4 hours. I counted these patients as nonresponders and recalculated the response rate for 4 hours.

Study 17: Percentage of patients with headache response					
	Placebo (N=139)	1 mg (N=140)	2.5 mg (N=297)	5 mg (N=279)	10 mg (N=283)
0.5 hours	14%	14%	16%	20%	20%
1 hour	24%	33%	43%*	44%*	50%*
2 hours	32%	50%*	63%*#	65%*#	65%*#
4 hours [a]	28%	52%*	70%*#	69%*#	70%*#

* p value < 0.05 when compared to placebo
# p value < 0.05 when compared to 1 mg
[a] 78 patients took escape medication prior to the 4 hour time point (17 on placebo, 10 on 1 mg, 18 on 2.5 mg, 20 on 5 mg, 13 on 10 mg)

Subgroup analyses: The sponsor performed analyses for sex, age, and weight and found no significant differences between groups. There were small numbers of patients in many of the groups leading to variable responses. An analysis by race was not performed (note: 94% of the patients in the study were white). They also analyzed the data by migraine history. There did not appear to be significant differences when taking into account migraines associated with menses, usual duration of migraines or number of ER visits during migraine headaches. Patients with > 4 migraines per month consistently had lower response rates than patients with 2 or 3 headaches per month. Patients who responded to other treatments also had higher response rates in the doses ≥ 2.5 mg. Patients with moderate headaches had higher response rates than patients with severe headaches. There did not appear to be differences in patients who took preventative medication, who had auras and who had different durations of headache. 14 patients were < 18 years old.

Study 17: Subgroup analyses for headache response at 2 hours		
Parameter	Placebo (N=140)	2.5 mg (N=298)
Race-non White (N)	7	15
Sex-male (N)	15	33
headache relief at 2 hours	20%	58%
Sex-female	124	265
headache relief at 2 hours	33%	64%
Age < 18 (N)	1	3
Age ≤ 30 (N)	15	35
headache relief at 2 hours	33%	54%
Age > 50 (N)	22	45
headache relief at 2 hours	41%	73%
Age 31 to 50 (N)	102	218
headache relief at 2 hours	29%	63%

Second dose efficacy: Patients who continued to have a headache or had a recurrence of headache pain including mild pain were given the option of using a second dose of study treatment. The sponsor designed the study to evaluated the efficacy of the second dose. The primary comparison for the determination of the efficacy was the response rate 2 hours after the second dose. In order the make the comparison valid, the sponsor randomizing patients to either take a second dose of the original study treatment or take placebo. I took all patients who received a second dose and excluded those patients who took rescue prior to the 2 hour endpoint assessment. In the following table, I have summarized the comparison of the response rates 2 hours after the second dose.

Study 17: Response rate of patients randomized to second treatment					
Second dose randomization	Placebo (N=61)	1 mg (N=68)	2.5 mg (N=125)	5 mg (N=111)	10 mg (N=84)
Response rate of patients randomized to placebo (N)	31% (61)	42% (36)	45% (60)	53% (58)	61% (41)
Response rate of patients randomized to the original study treatment		50% (32)	57% (65)	62% (53)	70% (43)

I calculated the response rate to the second treatment for those patients with moderate or severe headaches prior to the treatment with the second dose.

Response rate of patients randomized to second treatment in patients with moderate or severe headaches					
Second dose randomization	Placebo (N=52)	1 mg (N=56)	2.5 mg (N=90)	5 mg (N=78)	10 mg (N=62)
Response rate of patients randomized to placebo (N)	21% (52)	32% (31)	31% (44)	43% (42)	57% (30)
Response rate of patients randomized to the original study treatment		44% (25)	50% (46)	47% (36)	69% (32)

In order to increase the power of the study to detect a difference with the second dose, the sponsor prospectively proposed to combine all active treatment groups that showed efficacy and compare the combined group with placebo. I did combine all active treatment groups and compared the second dose efficacy. 193 patients were randomized to active treatment and 195 were randomized to placebo. The mean response rate was 60% and 50% for the active and placebo groups, respectively. The p value associated with my comparison was > 0.05. If I added the patients who received placebo initially, the response rate for all patients taking placebo for their second dose dropped to 46%. Now, a comparison with the active group yielded a p value of < 0.05. See the following table for a summary of the

results.

Study 17: Response rate for second dose combining active treatment groups		
	Data set excluding patients originally randomized to placebo	Data set including patients originally randomized to placebo
Placebo response rate (N)	50% (193)	46% (256)
Active drug response rate (N)	60% (195)	60% (193)
P value	>0.05	< 0.05

To evaluate the efficacy of a second dose given that a patient either was a non responder to the initial dose at 4 hours or had headache recurrence, I eliminated all patients who took placebo as their first dose. I examined two subgroups, those patients who took the second dose because they were non responders at 4 hours post the initial dose and those who took the second dose because of headache recurrence following response at 4 hours. The protocol allowed patients with mild pain on headache recurrence to treat with a second dose. I calculated the headache response rates 2 hours after dosing with a second dose for patients who treated any headache and for those who only treated a moderate or severe headache. The results are summarized in the following tables:

Study 17: Response rate 2 hours after second dose in patients who were non responders 4 hours following the initial dose	
	Response rate
1 mg group	
Second dose-placebo (N=20)	25%
Second dose- 1 mg (N=19)	42%
2.5 mg group	
Second dose-placebo (N=22)	36%
Second dose- 2.5 mg (N=24)	46%
5.0 mg group	
Second dose-placebo (N=23)	43%
Second dose- 5.0 mg (N=22)	41%
10.0 mg	
Second dose-placebo (N=14)	50%
Second dose- 10 mg (N=16)	56%
1 mg, 2.5, 5 and 10 mg groups combined	
Second dose-placebo (N=79)	38%
Second dose- active (N=81)	46%

Response rate 2 hours after second dose in patients who were responders 4 hours following the initial dose with headache recurrence including mild pain.	
	Response rate (%)
1 mg group	
Second dose-placebo (N=16)	63%
Second dose- 1 mg (N=13)	62%
2.5 mg group	
Second dose-placebo (N=38)	50%
Second dose- 2.5 mg (N=41)	63%
5.0 mg group	
Second dose-placebo (N=35)	60%
Second dose- 5.0 mg (N=31)	77%
10.0 mg	
Second dose-placebo (N=27)	67%
Second dose- 10 mg (N=27)	78%
1, 2.5, 5 and 10 mg groups	
Second dose-placebo (N=116)	59%
Second dose- active (N=112)	71%

Response rate 2 hours after second dose in patients who were responders 4 hours following the initial dose with headache recurrence excluding mild pain.	
	Response rate (%)
1 mg group	
Second dose-placebo (N=11)	45%
Second dose- 1 mg (N=7)	57%
2.5 mg group	
Second dose-placebo (N=25)	32%
Second dose- 2.5 mg (N=22)	55%
5.0 mg group	
Second dose-placebo (N=22)	50%
Second dose- 5.0 mg (N=15)	53%
10.0 mg	
Second dose-placebo (N=17)	65%
Second dose- 10 mg (N=18)	78%
1, 2.5, 5 and 10 mg groups	
Second dose-placebo (N=75)	47%
Second dose- active (N=62)	61%

Secondary outcome measures:

Headache free rates at 4 hours post initial dose: I took all patients with no pain at 4 hours. There were 96 patients with no ratings at 4 hours (13 on placebo, 14 on 1 mg, 187 on 2.5 mg, 24 on 5 mg and 28 on 10 mg). I included these patients in the non responder group. The pain free rates at 4 hours is included in the summary of secondary outcome table.

Maintenance of headache response defined as headache response at 4 hours without recurrence or rescue/second dose over the 24 hour period: I took all responders to the initial dose at 4 hours for the denominator. Patients who did not take rescue or a second dose or who did not have a recurrent moderate or severe headaches were included in the numerator. The percentage of patients is in the summary table.

Use of rescue: I took all patients who had time to rescue data. The percentage of patients who used rescue treatments is in the summary table.

Time to rescue treatment: I took the mean time to rescue and included the results in the summary table.

Use of second dose: I took all patients who had a time from first dose and second dose and included the results in the summary table.

Time to second dose: I took the mean time to the second dose and included the results in the summary table.

Use of rescue and/or second dose: I took patients who used either rescue and/or a second dose and included the results in the summary table.

Recurrence of headache: I took the number of patients with headache response at 4 hours and counted the number of these patients who had a return of pain to mild or moderate. I calculated the number of these patients with severe pain and the mean time to recurrence. These numbers are in the secondary outcome table.

Study 17: Summary of secondary outcome measures					
	Placebo (N=140)	1.0 mg (N=141)	2.5 mg (N=298)	5 mg (N=280)	10 mg (N=285)
% of patients headache free rate at 4 hours	9%	30%	41%	46%	53%
% of patients without recurrent headache or rescue/second dose	14%	27%	33%*	39%*	47%*
% of patients with nausea at 240 minutes	40%	24%	20%	20%	17%
% of patients with vomiting at 240 minutes	9%	3%	4%	2%	1%
% of patients with photophobia at 240 minutes	65%	45%	32%	25%	25%
% of patients with phonophobia at 240 minutes	57%	35%	24%	22%	24%
% of patients using a rescue medication	69%	46%	44%	41%	36%
Time (hours) to use of rescue medication	6.0	7.4	9.1	9.8	10.6
% of patients using a second dose of study treatment	52%	52%	47%	43%	33%
Time (hours) to use of second dose	5.5	6.7	9.4	9.2	9.4
% of patients using rescue medication and/or a second dose	84%	71%	64%	59%	49%
Time (hours) to use of rescue medication and/or second dose	2.8	3.9	5.5	5.7	6.6
Number of patients with recurrence/ Number of patients with headache relief at 4 hours (%)	17/39 (44%)	38/73 (52%)	102/209 (49%)	84/193 (44%)	81/200 (40%)
Mean time (hours) to recurrence	14.7	14.3	14.4	13.3	15.2
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (mod or severe) (%)	13/32 (41%)	18/48 (38%)	31/102 (30%)	21/82 (26%)	29/72 (40%)

*P value < 0.05

Comments: Study 17 was a well controlled study that evaluated the efficacy of 1, 2.5, 5 and 10 mg doses. The study designed allowed evaluation of an initial dose as well as a second dose of the drug to treat the same headache. The study was overpowered to detect the efficacy of the initial dose of the drug and was underpowered to assess the efficacy of the

second dose. The primary outcome measure was the headache response rate at 2 hours defined as headache pain going from moderate or severe to mild or no pain. The response rate for all doses was significantly better than placebo at 2 and 4 hours post dose. The response rates seen with doses ≥ 2.5 mg was significantly better than those seen with the 1 mg dose. I agree with the sponsor that these results support the conclusion that, one, the drug is effective, two, doses ≥ 2.5 mg are more effective than doses of 1 mg and, three, doses of 2.5, 5 and 10 mg are not distinguishable statistically.

To assess the second dose of the drug, the sponsor compared all effective doses against placebo and found a statistically significant increase in response rate for those patients treated with active drug compared to those treated with placebo. I found that this comparison may be misleading in that the sponsor is not recommending doses of 5 and 10 mg and that inclusion of patients initially assigned to placebo may be an unfair comparison, favoring the drug. It does not take into account that there may be continued effects of the drug following the second dose so that some of the benefit attributed to the second dose may be related to the first dose. This is a carry over effect seen with cross over studies with insufficient wash out periods between doses. A more even and clinically relevant comparison would be between patients who were initially non responders and were randomized to placebo or the original dose. The difference in response would be related to the second dose alone. In this analysis, the direction of change was in favor of the drug but did not achieve statistical significance except for the 10 mg dose. The lack of statistical significance is not unexpected because the study was not powered sufficiently to detect the difference. Possibly pooling data from studies with similar design would lead to a statistically significant difference.

Also important is the effect of the drug on the entire course of the migraine. The primary outcome measure only assesses the effect of the drug in the 2 to 4 hours following treatment. For the majority of patient, their headaches did not resolve with a single dose of treatment. Either patients did not respond by 4 hours or they had a recurrence of their headaches. Other observations from the time from 4 to 24 hours following treatment included the following: (1) Treatment of the drug did not appear to lead to an increase in frequency or severity of recurrent headaches. (2)

The drug did not appear to lead to an increase need for rescue medication and/or second dose of the drug. Numerically, the percentage of patients with requiring rescue and the time to rescue was decreased. More patients on drug had relief of their headaches without recurrence and less had the need for rescue or a second dose of treatment when compared to those on placebo. (3) The percentage of patients with associated symptoms of migraines were lower in the patients receiving active treatment compared to those receiving placebo. Since all of these measures were secondary outcome measures, the statistical significance is difficult to assess because the alpha level for the comparisons were not adjusted for the number of comparisons.

For all of the measures, the direction was in favor of drug and almost always better as the dose increased. From this study, while doses from 1 to 10 mg are effective, the higher the dose the better the response. For the primary outcome measure, the difference between the 1 mg dose and the other doses appears to be statistically different.

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Study 42:

Following the completion of study 17, the sponsor noted that doses ≥ 2.5 mg had comparable efficacy but adverse events showed a trend to increase at doses > 2.5 mg. Since doses of 1 and 2.5 mg had similar adverse event profile, the sponsor concluded that the dose of 2.5 mg had the most favorable efficacy and safety profile. Study 42 was designed to confirm the efficacy of 2.5 mg. The outcome measures were similar to study 17. The first patient was enrolled on 12/95 and the last patient was discharged on 4/12/96.

Protocol:

Design: This was a multicenter, double blind, placebo controlled outpatient study comparing 2.5 mg and placebo in the treatment of a single migraine. Patients were randomized in a 2:1 ratio favoring active drug. Patients were allowed to take rescue medication 4 hours after receiving the study treatment. There was no second dose of active treatment offered.

Sample: 300 patients were to be enrolled at 25 centers.

Selection: Similar criteria were used in this study and study 17.

Schedule: Efficacy was assessed at 0, 1, 2, 4 and 24 hours following treatment.

Outcome: Headache severity: assessed at 0, 1,2,4 and 24 hours following treatment.

Associated symptoms: assessed at 0, 1,2,4 and 24 hours following treatment.

Time to meaningful relief: determined as a subjective assessment of the patient at 0,2,4 hours post treatment.

Activities impairment/health economics: assessed at 1,2,4 hours from treatment along with the time lost from paid employment.

Other treatments: noted from 48 hours prior to 24 hours following

treatment.

Analysis: Data sets: All patient population included all patients know to have taken drug and had data available following randomization and **Protocol preferred population included all who had reasonably followed all protocol requirements.**

Primary analysis: Proportion of patients with headache response (moderate or severe pain to mild or no pain) will be compared. The analysis will be adjusted for baseline characteristics that are not comparable between groups including age, sex, presence of aura, initial headache severity, duration of headache prior to treatment, etc.

Results:

Disposition: 327 patients were randomized, 219 to active treatment and 108 to placebo. 26 patients were excluded from the efficacy analysis (9 from the placebo group and 19 from the 2.5 mg group). 23 did not receive study treatment and 3 did not have information available post treatment. In the all patients data set there were 101 patients in the placebo group and 200 patients in the 2.5 mg group. The sponsor excluded patients from the per protocol group for taking escape medication within 2 hours of study treatment (9 patients in the 2.5 mg group and 4 in the placebo group), did not take medication within 12 hours of onset of headache (10 in 2.5 mg group and 3 in placebo group), assessments taken outside of the 2 hours window (3 in the 2.5 mg group and 2 in the placebo group.

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Study 42: Disposition of patients

	Placebo	2.5 mg	Total
Randomized	108	219	327
Did not receive study treatment	6	17	23
No post treatment assessments	1	2	3
All patient population	**101**	**200**	**301**
Took escape medication < 2 hours following study treatment	4	9	13
Did not take study treatment within 12 hours of headache	3	10	13
Assessments outside the 2 hours window	2	3	5
Per Protocol population	**92**	**178**	**270**

Demographics and baseline characteristics: The demographics and baseline characteristics were similar between groups. Some of these features are in the following table:

Study 42:Demographics and baseline characteristics for the All treated population			
	Placebo (N=101)	2.5 mg (N=200)	Total (N=301)
Mean age	40.2	40.7	40.5
% female	85%	85%	85%
% white	93%	96%	95%
% employed	80%	80%	80%
Mean weight	68.2 kg	70.1 kg	69.5 kg
% headache without an aura	70%	69%	69%
Mean number of headaches per month	2.9	2.9	2.9
Fair or good response to ASA/NSAIDS	52%	55%	55%
% current use of sumatriptan	17%	19%	18%
Fair or good response to oral sumatriptan	83%	79%	80%

Baseline headache: The characteristics for the baseline headache treated in the study are summarized in the following table:

Study 42: Baseline headache characteristics			
	Placebo	2.5 mg	Total
% with moderate pain	79%	76%	77%
% with no Aura	84%	82%	83%
% with nausea present	52%	49%	50%
Photophobia	89%	80%	83%
Phonophobia	69%	70%	70%
Mean number of hours from onset to treatment	3	3.9	3.6

Primary outcome measures:

The primary outcome measure was headache relief (no or mild pain) at 2 hours. The rate of headache relief was significantly higher in the group of patients on 2.5 mg compared to those patients receiving placebo. The rates are summarized in the following table. In this table, if a patient had taken escape prior to the treatment, I counted them as non responders.

Study 42: Percent of patients with relief (no or mild pain) following the initial treatment		
Hours post dose	Placebo (responders/N)	2.5 mg (responders/N)
1	26% (26/100)	33% (66/198)
2	35% (35/100)	60%* (119/197)
4	35% (32/94)	68%* (126/184)

*p< 0.05

To get a sense of the duration of effect, I calculated the percentage of patients with relief at 2 hours who had a recurrence of headache and/or used escape

medication up to 24 hours after dosing. The results are summarized in the following table.

Study 42: Course of patients with headache relief at 2 hours post dose		
	Placebo	2.5 mg
% of responders who had a recurrence of headache within 24 hours	43% (15/35)	31% (37/119)
% of responders who used escape medication	40% (14/35)	33% (39/119)
% of responders who used escape medication and/or had a recurrence	54% (19/35)	40% (48/119)

Subgroup analyses: The majority of patients were white females between the ages of 30 and 50. For the most part, the number of patients in the placebo group was too small to assess subgroups.The results of some subgroup analyses are summarized in the following table.

Study 42: Subgroup analyses for headache response at 2 hours		
Parameter	Placebo (N=101)	2.5 mg (N=200)
Race-non White (N)	7	9
Sex-male (N)	15	30
headache relief at 2 hours	53%	53%
Sex-female	86	170
headache relief at 2 hours	31%	60%
Age < 18 (N)	4	4
Age ≤ 30 (N)	19	40
headache relief at 2 hours	53%	62%
Age > 50 (N)	18	44
headache relief at 2 hours	22%	59%
Age 31 to 50 (N)	64	116
headache relief at 2 hours	34%	58%

Secondary outcome measures:

Headache free rates at 4 hours post initial dose: I took all patients with no pain at 4 hours. If there was no rating, I rated these patients as having pain.

Headache response without recurrence or rescue: I took all patients with a response to the initial dose at 4 hours. I excluded patients who took rescue or who had a recurrent headache.

Use of rescue: I took all patients who had time to rescue times that occurred prior to 24 hours after dosing.

Time to rescue treatment: I took the mean time to rescue.

Use of rescue: I took all patients, whether or not they had a response to treatment who used rescue.

Recurrence of headache: I took the number of patients with headache response at 4 hours and counted the number of these patients who had a return of pain and the mean time to recurrence. I calculated the number of these patients with severe pain with the recurrent headache as defined by the variable SEVAT4.

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Study 42: Summary of secondary outcome measures		
	Placebo (N=101)	2.5 mg (N=200)
% of all patients with headache free rate at 4 hours	12%	34%
% of all patients with relief at 4 hours without recurrent headache or rescue	14%	34%
% of patients with nausea at 240 minutes	41%	18%
% of patients with vomiting at 240 minutes		
% of patients with photophobia at 240 minutes	61%	31%
% of patients with phonophobia at 240 minutes	40%	26%
% of patients using a rescue medication	65%	40%
Time (hours) to use of rescue medication	9.7	10.4
Number of patients with recurrence/ Number of patients with headache relief at 4 hours (%)	16/33 (48%)	36/127 (28%)
Mean time (hours) to recurrence	9.1	13.5
Number of patients with severe recurrent headaches/ Number of patients with recurrent headaches (mod or severe) (%)	1/33 (3%)	4/127 (3%)

NDA 20-768
Zolmitriptan efficacy review

Study 18:

Protocol:

Design: This was a single dose, double blind, placebo and active controlled, parallel, outpatient study comparing 100 mg of sumatriptan with 5 mg of zolmitriptan. Patients were randomized in an 8:8:1 ratio to sumatriptan, zolmitriptan or placebo. Rescue treatments were allowed 2 hours after the study treatment.

Sample: 1170 patients with about 12 evaluable patients per center.

Selection: Patients age 18 to 65 who were having 1 to 6 headaches per month were enrolled. Previous users of sumatriptan were excluded. Patients have had at least 10 minutes freedom from an aura.

Schedule: Outcome assessments were collected at 0, 1, 2 and 4 hours post dose.

Outcome: The primary outcome measure is defined as headache response at 2 hours (moderate to severe headache to mild or no pain) without headache recurrence in 24 hours. There is no mention of use of rescue.

Secondary outcome measures include headache response at 1, 2 and 4 hours post dose, presence or absence of nausea, vomiting, photophobia and phonophobia, use of escape medication, headache recurrence and time to meaningful relief as defined by the patient.

Analysis: Logistic regression model will be used to compare sumatriptan and zolmitriptan.

Results:

Disposition: 1311 were randomized from 20 countries and 106 sites. 225 did not take study medication and 28 had no follow up data. There was a total of 1293 patients in the efficacy data base. The distribution of patients and protocol violations are summarized in the following table:

Study 18: Disposition and protocol violations			
	0 mg	5 mg	Sumatriptan
Randomized	74	615	624
Study medication not taken	17	105	104
Lost to follow up	1	6	9
Missing all data	1	9	8
Total patients in the efficacy data base	55	495	503
Headache mild at baseline	0	0	1
Took drugs prior to treatment			
Took rescue < 2 hours after dose	1	14	10
No assessment at 2 hours	1	17	25

Demographics and baseline characteristics: The demographics were similar between groups. The mean age was 38.2. 83% of the patients were female. 99% were white. 73% of the patients had migraines without an aura. 41% had severe headache at baseline. Patients waited around 3 hours prior to treating their headaches. 33 to 44% had severe headaches at baseline.

Efficacy outcome measures:

Primary outcome measure: The primary outcome measure was complete response. The definition did not include whether the patient's took rescue. The percentage of patients with complete headache response was 29, 43 and 45% for the placebo, zolmitriptan and sumatriptan groups, respectively. When analyzing the percentage of patients with headache relief at 2 hours and no recurrence of headache and no use of rescue, the difference between groups was not associated with a p value of < 0.05 when comparing all pairs using Tukey-Kramer.

The headache relief rates for each group are summarized in the following table:

Study 18: Headache relief rates (*comparison with placebo p value < 0.05)			
Time-post dose	0 mg N=55	5 mg N=495	Sumatriptan N=503
60 minutes	20	34	35*
120 minutes	44	59*	62*
240 minutes	40	73*	77*

Subgroup analyses: The majority of patients were white females between the ages of 30 and 50. For the most part, the number of patients in the placebo group was too small to assess subgroups.The results of some subgroup analyses are summarized in the following table.

Study 18: Subgroup analyses for headache response at 2 hours			
Parameter	Placebo (N=55)	5 mg (N=495)	Sumatriptan (N=503)
RACE			
Race-non White (N)	0	8	4
SEX			
Sex-male (N)	8	80	80
headache relief at 2 hours	50%	65%	65%
Sex-female	46	399	409
headache relief at 2 hours	43%	58%	61%*
AGE			
Age ≤ 30 (N)	16	118	129
headache relief at 2 hours	56%	60%	58%
Age > 50 (N)	3	60	62
headache relief at 2 hours	100%	62%	77%
Age 31 to 50 (N)	35	301	298
headache relief at 2 hours	34%	59%*	60%*

Secondary outcome measures: The sponsor described over 50 analyses on secondary outcome measures. This included analyses at each time point in the

study and for each variable. I have reviewed these outcome measures and have summarized a number of them in the following table.

Study 18: Summary of secondary outcome measures			
	Placebo (N=55)	5 mg (N=495)	Sumatriptan (N=503)
Headache free rate at 4 hours	13%	29%	30%
% of patients with nausea at 120 minutes	40%	31%	33%
% of patients with photophobia at 120 minutes	51%	34%	32%
% of patients with phonophobia at 120 minutes	49%	37%	34%
% of patients using a rescue medication	56%	38%	36%
Time (hours) to use of rescue medication	5.1	9.8	8.4
Number of patients with recurrence/ Number of patients with headache relief at 2 hours (%)	8/24 (33%)	73/28 (26%)	74/301 (25%)

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Study 006:

Protocol:

Design: This was a single center, inpatient, double blind, placebo controlled, parallel, dose ranging study evaluating the effects of a single dose of 0, 1, 5 or 25 mg in the treatment of a single attack. 2 hours after the first dose, patients were allowed to take a second dose. The use of the second dose was not randomized. Patients on placebo received 10 mg of the drug, patients on 1, 5 and 25 mg received as their second dose 15, 20 or 0 mg, respectively. If the patients did not take a second dose, they were allowed to take rescue treatment 3 hours after the first dose. If a patient took a second dose, they were allowed to take rescue 4 hours after the initial dose. Patients were discharged 4 hours after their last dose of study treatment.

Selection: Patients, age 18 to 55, were eligible for enrollment. Patients had to have an average of ≤ 6 migraines per month. Patients were otherwise healthy including no history of cardiac disease or high BP. Base line ECGs did not show evidence for cardiac disease. Patients were excluded if they used prophylactic medication. Before taking the study treatment, they had to have been headache free for 48 hours, had no analgesics for 6 hours and no aura immediately prior to taking the treatment. The headache had to be moderate to severe of ≤ 12 hours in duration.

Schedule: Headache symptoms were measured at 0, 0.5, 1, 2, 2.5, 3, 4, 6 and 24 hours post dose. Plasma levels were checked at 0, 0.5, 1, 2, 4 hours after the initial dose. If a second dose was taken, then levels were measured at 2.5, 3 and 6 hours.

Sample: Assuming a placebo rate of 25% and a response rate of at least of 60%, 30 patients were needed per group to have 80% power.

Interim: An interim analysis was performed 3 months after the first patient was enrolled. This was an administrative look to determine the dose for future studies.

Analysis: The primary outcome measure was the response rate at 2 hours. The analysis was performed on the data set of all patients randomized who received at least one dose of drug and had outcome measures available. Secondary outcomes included headache response at each time point, headache free at 2 hours, frequency of photophobia, nausea and vomiting, headache recurrence, use of escape medication.

Results:

Disposition: The study was conducted from 12/23/93 and was stopped early because of slow patient recruitment. A total of 84 patients were enrolled. The disposition of patients is summarized in the following table.

Study 006: Disposition of patients and protocol violations				
	Placebo	1 mg	5 mg	25 mg
Number of patients randomized-all efficacy data set	20	22	21	21
Vomited within 30 minutes of dosing	0	1	2	0
Treated mild headache	1	0	0	0
Protocol Preferred data set	19	21	20	21

Demographics and baseline characteristics: The sponsor did not find any significant differences between groups in the demographic profile or baseline characteristics. The mean age was about 42 with a range of 20 to 54. 80% were female and 98% were white. 63% of the patients had migraines without auras. The average number of migraines per month was 3.1. 92% of the patients were current users oral and/or subcutaneous sumatriptan. 75% reported good response on subcutaneous sumatriptan.

Primary efficacy measure: The percentage of patients with headache relief is summarized in the following table for the all patient data set. At 2 hours, the differences between the 5 and 25 mg treatment group and placebo was associated with a p value of < 0.05. There were no differences between active groups.

Study 006: Percentage of patients with headache relief

	Placebo (N=20)	1 mg (N=22)	5 mg (N=21)	25 mg (N=21)
1 hour	15	9	24	43
2 hours	15	27	**62***	**81***

* P value < 0.05

Subgroup analyses: The sponsor analyzed the data for effects on the following variables: age, severity of headache at baseline, weight, aura, duration from onset to first dose, sex, vomiting within 30 minutes of the first dose. These variables were not found to be significant in providing additional information about the headache response.

Secondary outcome measures: The sponsor analyzed the headache response at time points other than 2 hours, percentage of patients with no pain at 2 hours post dose, incidence of nausea, vomiting and photophobia, headache recurrence and use of escape medication. Some of the results are summarized in the following table:

Study 006: Summary of secondary outcome measures (using the sponsor defined protocol preferred data set)				
	Placebo (N=20)	1 mg (N=22)	5 mg (N=21)	25 mg (N=21)
% of patients headache free rate at 2 hours	5%	9%	14%	38%
% of patients with nausea at 2 hours	35%	59%	24%	10%
% of patients with photophobia at 2 hours	65%	59%	43%	29%
% of patients using a rescue medication	20%	23%	14%	10%

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Study 008:

Protocol:

Design: This was a multicenter, double blind, placebo controlled, parallel, outpatient study evaluating the efficacy of the treatment of a single headache with a single dose of 0, 5, 10, 15 or 20 mg. Patients will be randomized in a 1:2:2:2:2 ratio of 0, 5, 10, 15 or 20 mg, respectively. Escape medication was allowed 2 hours after the study treatment

Selection: Patients age 12 to 65 who, on average, had 1 to 6 migraines per month, were to be enrolled. The patients were otherwise healthy. Patients were to treat headaches with moderate to severe pain with a duration of < 6 hours. The patients were supposed to be migraine free for 72 hours prior to treating the headache. The patient must have been free of an aura for at least 10 minutes and the aura.

Schedule: Efficacy assessments were obtained at 0, 1 and 2 hours following the study treatment.

Sample: Assuming response rates for placebo and active drug to be 35 and 55%, respectively, 88% power and alpha level of 0.05, a minimal of 180 patients per active group and 90 in the placebo group. This will also provide 80% power to detect a 15% difference between active groups.

Outcome: Primary: Headache response defined as a reduction in headache pain from moderate or severe to mild or no pain at 2 hours following the initial dose.

Secondary:

Percent of patients with no pain at 2 hours
Headache response at 1 and 2 hours post treatment
Headache recurrence, defined as headache relief at 2 hours with return of moderate or severe pain.
Prevalence of migraine symptoms at 1 and 2 hours post treatment

use of escape medication

Analysis: Data sets include an all treated population consisting of all patients known to have taken any study medication. The sponsor noted that they may exclude some patients because of protocol violations.

Subgroups: sex, patients who did not vomit within 30 minutes of the treatment, took treatment within 2 hours of headache onset, Age, presence of aura, initial headache severity, weight, duration of headache at treatment and menstruation.

Results:

Disposition: The study was conducted from 9/15/93 to 7/6/94. A total of 1181 patients were randomized. The disposition of patients is summarized in the following table.

Study 008: Disposition of patients and protocol violations					
	Placebo	5 mg	10 mg	15 mg	20 mg
Number of patients randomized	126	265	262	270	258
Number of patients who did not take any study treatment	23	45	38	41	37
Number of patients without follow up data	4	7	10	14	11
Total patients in all patient efficacy data set	99	213	213	215	209
Took escape or 2nd tablet < 2 hrs after tablet 1	1	3	0	1	0
Other protocol violations [a]	10	31	22	20	21
Protocol Preferred data set	88	179	191	194	188

[a] 2 hours data outside the data window, vomited within 30 minutes of study treatment, missing evaluation criteria

Demographics and baseline characteristics: The sponsor did not find any significant differences between groups in the demographic profile or baseline characteristics. The mean age was 40.0 with a range of 18 to 65. 84% were

female and 99% were white. 69% of the patients had migraines without auras. The average number of migraines per month was 2.9. 34% of the patients were current users oral and/or subcutaneous sumatriptan. 76% reported good response on subcutaneous and 62% reported a good response on oral sumatriptan. 57% of the patients had a moderate headache at baseline with a mean duration of 2.9 hours between onset and treatment. 64% had nausea, 78% had photophobia and 74% had phonophobia.

Primary efficacy measure: The percentage of patients with headache relief is summarized in the following table for the all patient data set. At 2 hours, the differences between each active treatment group and placebo is associated with a p value of < 0.05. There were no differences between groups.

Study 008: Percentage of patients with headache relief					
	Placebo (N=99)	5 mg (N=213)	10 mg (N=213)	15 mg (N=215)	20 mg (N=209)
1 hour	16	44	40	42	50
2 hours	21	61*	67*	67*	74*

*P value < 0.05

Subgroup analyses: The sponsor performed analyses on the following subgroups, sex, age, weight, use of oral contraceptives, use of preventative treatments and presence of aura and found that these variables did not effect the headache response at 2 hours. There were small numbers of patients in many of the groups leading to variable responses for a number of subgroups. An analysis by race was not performed (note: 94% of the patients in the study were white). Patients with moderate headaches had higher response rates than patients with severe headaches. The results of the headache relief rates at 2 hours by severity of headache at baseline is summarized in the following table:

Study 008: Percentage of patients in the all patient data set with headache relief at 2 hours by severity of baseline headache					
	Placebo (N=99)	5 mg (N=213)	10 mg (N=213)	15 mg (N=215)	20 mg (N=209)
Moderate	22	71	79	75	82
Severe	16	60	59	61	69

Secondary outcome measures: The sponsor calculated the secondary outcome measures using the protocol preferred data set.

Headache free rates at 2 hours post initial dose: The sponsor took all patients who had no pain at 2 hours.The pain free rates at 4 hours is included in the summary of secondary outcome table.

Use of rescue: The sponsor took all patients who used rescue and calculated the mean time to rescue.

Recurrence of headache: The sponsor took the number of patients with headache response at 2 hours and counted the number of these patients who had a return of pain to mild or moderate. They did not take into account that the patient may have taken rescue medication. The results are in the summary table:

Study 008: Summary of secondary outcome measures (using the sponsor defined protocol preferred data set)					
	Placebo (N=88)	5 mg (N=179)	10 mg (N=191)	15 mg (N=194)	20 mg (N=188)
% of patients headache free rate at 2 hours	1	39	39	43	47
% of patients without recurrent headache or rescue/second dose	7	49	51	55	55
% of patients with nausea at 2 hours	34	27	31	32	29
% of patients with photophobia at 2 hours	59	32	35	37	27
% of patients with phonophobia at 2 hours	55	31	30	34	28
% of patients using a rescue medication	81	53	50	42	41
Time (hours) to use of rescue medication	3.7	7.4	9.8	8.2	8.9
Number of patients with recurrence/ Number of patients with headache relief at 2 hours (%)	11/17 (65%)	32/118 (26%)	39/136 (28%)	28/134 (21%)	42/145 (29%)
Mean time (hours) to recurrence	8	14.6	15.4	13.0	15.5

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Study 015:

Protocol: This was an open label study to evaluate the long term safety and efficacy of the drug. Patients treat headaches over the course of a year with 5 mg. They were allowed to use a second dose for persistent or recurrent pain.

Results:

Disposition: 2058 patients treated 31,579 headaches over the course of 1 year. 1835 patients treated moderate to severe headaches. The mean number of headaches treated was 15 (range: 1 to 124) with an average of 12 days between treatments (range: 4 hours to 280 days).

Headache response 2 hours after treatment: The results are summarized by the sponsor in the following table:

Data Summary 62
Headache Response[1] at 2 Hours Post-Treatment
For Patients in the Long-Term Uncontrolled 311C90 Study (015)

Dose	Headache Response	Attack Number 1 n	(%)	Attack Number 5 n	(%)	Attack Number 15 n	(%)	Attack Number 30 n	(%)	Attack Number 45 n	(%)
Post Tablet A	N	1835		1171		609		233		79	
	No	481	(26%)	271	(23%)	110	(18%)	38	(16%)	12	(15%)
	Yes	1354	(74%)	900	(77%)	499	(82%)	195	(84%)	67	(85%)
Post Tablet B	N	619		440		240		97		45	
	No	169	(27%)	103	(23%)	37	(15%)	13	(13%)	6	(13%)
	Yes	450	(73%)	337	(77%)	203	(85%)	84	(87%)	39	(87%)

Individual response rates: The sponsor calculated the overall response rate for each patient by dividing the number of successful responses (response at 2 hours) by the total number of attacks treated. For patients treating at least 5 headaches, 86% had an overall response rate of ≥ 60%. 67% had an overall response rate of ≥ 80%.

Randy Levin, M.D.
Neurology Team Leader

cc:
Original NDA

Review and Evaluation of Clinical Data

NDA	**20-768**
Sponsor:	**Zeneca**
Drug:	**zolmitriptan**
Proposed Indication:	**migraine**
Material Submitted:	**NDA**
Correspondence Date:	**11/26/96**
Date Received / Agency:	**11/29/96**
Date Review Completed	**5/1/97**

Table of Contents

1. Review Sources

This is the safety review for zolmitriptan tablets. The sources used for the review are outlined in Table 1.

Table 1: NDA Materials used in Review

Source	Submission Date	Material
Vol. 1-2	11/26/96	Index, Summary, proposed labeling
Electronic Submission	11/26/96	Integrated Summary of Safety, SAS transport file datasets for study 015, 006, 008, 017, 018, 042
Vol 119	11/26/96	Study Summaries
Vol 157	11/26/96	Study 15 Summary
Vol 211-212	11/26/96	ISS
4 Mo. Safety Update	3/24/97	Vol. 1-4

2. Background

2.1 Indication

Zolmitriptan is a $5HT_{1D}$ receptor agonist. It is indicated for the acute treatment of migraine with or without aura.

2.2 Important Information from Pharmacologically Related Agents

Zolmitriptan is pharmacologically similar to sumatriptan. Because of the potential for this class of compounds (5-HT $_{1D/1B}$ agonists) to cause coronary vasospasm, they should not be used in patients with coronary artery disease (CAD) or in patients in whom unrecognized CAD is likely without a prior evaluation.

2.3 Administrative History

Original IND received from Burroughs Wellcome	*4/28/94*
End of Phase II Meeting	*1/31/95*
Pre-NDA Meeting	*6/19/96*

The IND for zolmitriptan tablets was submitted by Burroughs Wellcome Co. on 4/28/94. In May 1994, the Division requested more time to review the IND and the sponsor agreed to delay U.S. clinical trials. The agency recommended various changes to the Investigator's Brochure on 7/27/94, and recommended additional work to characterize the active metabolite. The U.S. development program began during the summer of 1994. The End of Phase II meeting was held between the FDA and Burroughs Wellcome on 1/31/95.

With the merger of Burroughs-Wellcome and Glaxo, the rights for zolmitriptan were transferred to Zeneca. A pre-NDA meeting of Division, Glaxo-Wellcome and Zeneca representatives was held on 6/19/96 and the following agreements were reached:

1. The oncogenicity study design was considered adequate, subject to final review of the data.
2. Pending final review of data, the lowest dose to be included in the labeling is 2.5 mg, with both 2.5 and 5 mg tablets available.

3. Using ICH as a reference, the Division outlined the general expectations for long-term safety, *i.e.*, 300 patients treating an average of two or more headaches per month for six months, and 100 patients treating at least two or more headaches per month for one year.
4. Agreements were reached regarding format, organization, and content of the Integrated Summary of Efficacy and the Integrated Summary of Safety, as well as the electronic data files for the medical, biopharmaceutics and statistical reviewers.

2.4 Proposed Labeling

A brief review of the important clinical sections of the proposed labeling is included here. The more comprehensive review of the labeling is in Section 10, page 68.

2.4.1 Indication

Zomig™ is indicated for the acute treatment of migraine with or without aura.

2.4.2 Dosing

Zomig™ should be taken at the earliest onset of a migraine headache. The recommended dose to treat a migraine attack is 2.5 mg. For persistent or recurrent symptom, another 2.5 mg tablet is recommended, but should not be taken within 2 hours of the first dose. If 2.5 mg doses do not provide adequate relief, subsequent attacks may be treated with the 5 mg dose. The maximum recommended dose is 15 mg in a 24 hour period.

2.4.3 Treatment of Special Populations

Safety and efficacy in the elderly (> 65 yrs) have not been systematically evaluated. The pharmacokinetic profile in the elderly is similar to that seen in younger patients.

No change in dose is recommended in renal impairment

The pharmacokinetic profile has not been studied in patients with hepatic impairment.[1]

Safety and efficacy in pediatric patients have not been established.

2.4.4 Use with Other Drugs

Concomitant use of other 5-$HT_{1D/1B}$ agonists (e.g. sumatriptan, methysergide) within 12 hours of Zomig™ treatment is not recommended[2].

2.4.5 Drug Interactions

MAO inhibitors increase the systemic exposure to zolmitriptan and therefore caution should be taken during co-administration.

Pharmacological effects on blood pressure were unaffected with concomitant use of fluoxetine 20 mg/d for 4 weeks.

There were no interactive effects on blood pressure or pulse rate following administration of propranolol with zolmitriptan.

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[1] This statement was made prior to the submission of the results of Study 030, which was submitted with the abbreviated 4 month safety update and is described in section 7.5.2, page 35. C_{max} appears to be roughly 50% higher in liver disease patients.

[2] Sumatriptan labeling recommends a 24 hour interval between zolmitriptan administration and ingestion of these other agents.

In a small group of healthy individuals, concomitant administration of zolmitriptan with ergotamine/caffeine was well tolerated by volunteers and did not result in any increase in adverse events or blood pressure changes as compared to zolmitriptan alone.

After concurrent administration of zolmitriptan and 1 g acetaminophen, zolmitriptan AUC and C_{max} were both increased by 11% and those of acetaminophen were decreased by 31% and 11%, respectively.

Metoclopramide (single 10 mg dose) had no effect on the pharmacokinetics of zolmitriptan or its metabolites.

2.4.6 Special Safety Concerns

Zomig™ should not be given to patients with uncontrolled hypertension.

Zomig™ is contraindicated in patients who are hypersensitive to zolmitriptan or any of its inactive ingredients.

Zomig™ should not be administered to patients with basilar or hemiplegic migraine. Care should be taken to exclude other potentially serious neurological conditions.

Because of the potential of this class of compounds (5-$HT_{1D/1B}$ agonists) to cause coronary vasospasm, Zomig™ should not be given to patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or to patients with Prinzmetal's angina. Also, patients with symptoms or signs consistent with ischemic heart disease should not receive Zomig™.

Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive Zomig™

Caution should be taken when co-administering zolmitriptan and MAO-A inhibitors.

Zomig™ should not be used to treat migraine prophylactically.

Concomitant use of other 5-$HT_{1D/1B}$ agonists (e.g. sumatriptan, methysergide) within 12 hours of Zomig™ treatment is not recommended[3].

2.4.7 Monitoring

No specific monitoring is advised.

2.5 Foreign Marketing

Zolmitriptan has not been marketed outside the United States.

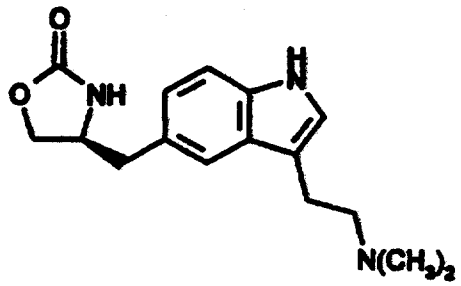
3. Chemistry, Manufacturing and Controls

Zolmitriptan is a white to almost white powder. The chemical structure is shown in Figure 1.

[3] Again, this should be 24 hours to increase the safety margin and to conform with sumatriptan labeling.

Generic Name: zolmitriptan
Chemical Name: S-4-[[3-[2-Dimethylamino)ethyl]-1H-indol-5-y1]methyl]-2oxazolidinone
Alternative Name: 311C90
Molecular Formula: $C_{16}H_{21}N_3O_2$
Molecular Weight: 287.36

Figure 1: Chemical Structure, Zolmitriptan



Solid state stability studies have been done on three batches of zolmitriptan at a range of storage conditions for up to 18 months. The results indicate the compound is very stable in the solid state. No significant changes were observed after 6 months at 50°C, 6 months in an open jar at 40°C, 12 months at 30°C, or 18 months at 25°C. Based on these data, a retest date of 2 years when stored below 30°C is considered appropriate.

4. Animal Pharmacology & Toxicology

4.1 Pharmacology

Zolmitriptan is a potent, selective $5HT_{1D}$ receptor agonist, which exhibits low or no affinity at a wide range of other monoamine receptors, including other 5HT subtypes. In isolated blood vessels, it is a "$5HT_{1D}$-like" receptor partial agonist, causing concentration related contractions similar to those obtained with sumatriptan.

Zolmitriptan (0.3-100 µg/kg) causes a decrease in carotid arterial blood flow and an increase in carotid arterial vascular resistance. These cranial vascular effects are similar to those seen with sumatriptan, although zolmitriptan is 2-3 times more potent.

The potent cranial vascular activity of zolmitriptan does not extend to the remainder of the cardiovascular system. In experimental animals, doses of zolmitriptan (>100 µg/kg), in excess of those required to constrict cranial arteries, were needed to elicit other systemic cardiovascular effects (predominantly increases in BP, and heart rate). Doses up to 1 mg/kg in other major systemic vascular beds, including pulmonary and coronary circulation had little or no effect. The overall systemic cardiovascular profile of zolmitriptan is similar to that of sumatriptan.

4.2 Toxicology

Oral and i.v. toxicity studies were done in rats and mice. The approximate lethal oral dose is 1000 mg/kg in mice and 1000-1500 mg/kg in rats. Clinical signs included convulsions, muscle spasms, dyspnea, ataxia, and pink extremities. The approximate lethal i.v. dose was 50-100 mg/kg in both species.

A one month toxicity studies in rats showed a slight increase in thyroid weight without concomitant histologic changes. Renal and urothelial inflammation in a very small number of high dose animals were seen, and were considered equivocal. The no toxic effects dose was 100 mg/kg/day.

A one month oral toxicity studies in beagles was done at 5, 25, and 100 mg/kg/day. Clinical signs included abnormal vocalization, mydriasis, excessive drinking, and abnormal posture at all dose levels. One high dose female exhibited convulsions. No treatment related histologic findings were evident. All animals in the recovery group were normal 4 weeks after dosing. The no toxic effect dose was considered to be 25 mg/kg/day.

A six month oral toxicity studies in rats was done at 25-400 mg/kg/day. Twenty-three (23) of 60 high dose animals died and post-mortem exams failed to disclose any characteristic changes. Flushed extremities were noted at all dose levels. There was slight liver and thyroid hypertrophy in the high dose group.

A six month oral toxicity study in beagles (5-100 mg/kg/day) revealed clinical signs similar to the one month study. One 25 mg/kg/day male was killed after a series of convulsions and self mutilating behavior.

A 12 month oral toxicity study in dogs (5-100 mg/kg/day) revealed clinical signs similar to the one and 6 month studies. Aggressive behavior was seen in some animals, requiring the sacrifice of 2 animals. One high dose male was found dead on day 280 without a specific cause found. A slight increase in adrenal weight was seen at termination in other animals without histologic changes. The no toxic effect dose was considered to be 25 mg/kg/day.

Carcinogenicity bioassays have been conducted in rats and mice at the highest tolerated dose, 400 mg/kg/day. Males showed benign thyroid follicular adenomata and follicular hyperplasia. These changes were not seen in females, or at other dose levels in either gender.

Teratology studies in rats and rabbits showed no induction of fetal abnormalities. A fertility/reproduction study and a peri- post-natal study have been conducted in rats at doses up to 400 mg/kg/day without evidence of adverse events in either study at any dose level.

Five genetic toxicity studies have been conducted. An Ames test was negative. In CHO cells, zolmitriptan was non-mutagenic. An unscheduled DNA synthesis assay was negative at all doses including the highest tested (1000 mg/kg). In a human lymphocyte assay, zolmitriptan induced clastogenic effects at concentrations > 250,000 ng/mL.

In conclusion, hazards of zolmitriptan have been delineated in a wide range of studies and are apparent only at exposures in excess of those likely to be encountered clinically.

5. Clinical Data Sources

5.1 Primary Data Sources

5.1.1 Study Type

Sponsor Table 2 lists the studies contained in this NDA. It represents the clinical zolmitriptan development program.

Table 2: Zolmitriptan Studies contained in the NDA

Study	Design	N	Country
	Clinical Pharmacology Studies		
ADME, Bioequivalence, Food Interaction			
011	ADME, Open Label	6	UK
025	Bioequivalence, OL, crossover	24	Netherlands
044	Food interaction, dose proport., OL, crossover	12	Netherlands
Pharmacokinetics Studies (Volunteers)			
001	PK, PD, tolerability, dose-escalation, DB, crossover	12	UK
009	PK, PD, tolerability, dose-escalation, DB, crossover	13	UK
014	PK, tolerability, DB, crossover	12	UK
023	PK, PD, DB, crossover	13	UK
028	PK, OL, crossover	8	UK
311C-1 (NW-1)	PK, PD, tolerability, dose-escalation, DB, crossover	12	Japan
311C-2 (NW-2)	PK, PD, tolerability, dose-escalation, DB, crossover	12	Japan
Special Population Studies			
012	PK, PD, tolerability, young vs. elderly, DB, crossover	27	UK
013	PK, PD, controlled hypertension, DB, crossover	33	US
024	PK, PD, tolerability, renal impairment, OL, parallel	31	France
030	PK, PD, tolerability, hepatic impairment, OL, parallel	30	[ongoing]
Drug Interaction Studies			
010	PK, PD, drug interaction, DB, crossover	12	UK
021	PK, tolerability, drug interaction, DB, crossover	14	UK
033	PK, drug interaction, OL, crossover	15	UK
034	PK, PD, drug interaction, DB, crossover	13	UK
035	PK, PD, drug interaction, DB, crossover	20	US
038	PK, drug interaction, OL, crossover	12	UK
039	PK, PD, drug interaction, DB, crossover	14	France
Bioavailability Studies-Intravenous			
016	PK, tolerability, OL, crossover	12	UK
045	PK, OL, crossover	20	Netherlands
Intranasal Studies			
032	PK, PD, tolerability, dose-escalation, DB, crossover	12	UK
041	PK, OL, crossover	12	UK
	Clinical Trials		
Controlled Trials			
006	Double-blind, PBO, parallel, inpt, single attack	84	Netherlands
008	Double-blind, PBO, parallel, outpt, single attack	1181	Multinational
017	Double-blind, PBO, parallel, outpt, single attack	1141	US
042	Double-blind, PBO, parallel, outpt, single attack	301	US
Supportive Studies			
002	Open Label, uncontrolled, inpt, single attack	18	Belgium
007	Open Label, uncontrolled, crossover, inpt, single attack	20	Denmark
015	Open Label, uncontrolled, outpt, long-term, multiple attack	2058	Multinational
018	Double-blind, PBO & active ctr, parallel, outpt, sgl attack	1311	Multinational
026	Double-blind, PBO, crossover, outpt, multiple attack	30	UK

Thirty-one (31) zolmitriptan studies with 4,003 unique subjects (volunteers and migraineurs) contributed to the safety data. Subjects received almost 50,000 oral doses of zolmitriptan administered across a dose range of 0.5 - 50 mg. Over 2,000 patients participated for up to one year in study 015. Sponsor Table 3 divides the 31 studies into 4 broad based categories based on study type.

Table 3: Listing of Study Numbers by Study Type

Study Category	Study Type	Study Number(s)
Clinical Pharmacology	22 Clinical Pharmacology Studies (oral, I.V., intranasal, special population, drug-drug interaction)	001, 009, 010, 011, 012, 013, 014, 016, 021, 023, 024, 025, 028, 032, 033, 034, 035, 038, 039, 041, 044, 045
Placebo Controlled Treatment Studies	Single Attack, inpatient	006
	Single attack, single dose, outpatient	008, 018, 042
	Single attack, optional second dose, outpatient	017
Uncontrolled Treatment Studies	Single attack, single dose, inpatient	002, 007
	Multiple attack, optional second dose, long-term outpatient	015
Placebo Controlled Acute Prevention Study	Multiple attack, optional second dose, outpatient, during aura	026

5.1.2 Demographics

A total of 318 unique individuals participated in the Clinical Pharmacology studies (24 of which participated in more than one study). A total of 3,538 unique subjects participated in the five placebo-controlled treatment studies, and 117 unique subjects received zolmitriptan in the three uncontrolled treatment studies. Finally, 30 subjects took zolmitriptan during the aura phase as prevention for a headache in study 026. Overall, 4,003 unique individuals are included in the database. This information is summarized in sponsor generated Table 4.

Table 4: Unique Subjects Treated with Zolmitriptan in All Studies

Study Category	Number of Studies	Total No. of Unique Subjects	No. of Subjects in Multiple Studies
Clinical Pharmacology	22	318	29
Placebo Controlled	5	3,538	0
Uncontrolled	3	117	1,979
Prevention	1	30	0
Totals	**31**	**4,003**	**2,008**

In general, volunteers in the Clinical Pharmacology studies were healthy males and females. In the patient treatment studies, the subjects were males and females with an established history of migraines with or without aura, as defined by the International Headache Society. Patients were required to have a migraine history of greater than one year, with an age of onset of less than 50 years, and to have a history of 1-6 migraines per month for the preceding 6 months. In addition, patients had to have screening laboratory values in the acceptable ranges, and be without evidence of ischemic heart disease, arrhythmia, or accessory pathways, based on a 12 lead ECG.

The majority of patients were female, and between the ages of 18 to 65. In the clinical trials, females comprised 80-88% of the subjects. This is in contrast to the 2:1 female to male ratio present in the general population. The mean age in the clinical pharmacology studies (33.9) was younger than in the clinical trials (40.5). The racial composition was predominantly white. Sponsor generated Table 5 summarizes the demographic characteristics of the zolmitriptan exposed population.

Table 5: Demographic Characteristics of Study Population Exposed to Zolmitriptan

Treatment	No. of Subject Exposed	Gender		Age (yrs)	Weight (Kg)	Race		
		Male (%)	Female (%)			White (%)	Black (%)	Other (%)
Clinical Pharmacology Studies								
Oral	291	56	44	35.3 (18-76)	70.6 (47-99)	90	5	5
Intravenous	32	50	50	25.7 (19-38)	72.7 (52-95)	94	3	3
Intranasal	24	58	42	27.8 (19-42)	71.2 (55-91)	92	0	8
Patient Studies for Migraine Headache Treatment: Placebo-Controlled								
Inpt, opt 2nd dose	79	20	80	42.2 (20-54)	68.8 (38-95)	97	0	3
Outpt, single dose	1,550	16	84	39.6 (13-66)	66.7 (40-118)	98	<1	<1
Outpt, opt 2nd dose	1,004	12	88	41.3 (12-66)	70.9 (33-173)	94	4	2
Patient Studies for Migraine Headache Treatment: Uncontrolled								
Outpt, mult. Attack	2,058	14	86	40.9 (12-66)	68.0 (34-173)	97	2	1
Inpt, single dose	38	13	87	35.6 (18-50)	64.3 (50-102)	100	0	0
Patient Studies for the Acute Migraine Headache Prevention: Placebo Controlled								
Outpt, 2 attacks, opt 2nd dose	30	17	83	41.8 (24-60)	72.0 (46-103)	100	0	0

5.1.3 Extent of Exposures

Sponsor generated Table 6 summarizes the subject exposures to zolmitriptan and placebo in the Clinical Pharmacology studies. In these studies, 316 unique subjects received a total of 993 exposures to zolmitriptan and 148 exposures to placebo. All 316 subjects received zolmitriptan tablets, or another oral formulation (capsule, solution, or sublingual tablet) with a total of 148 exposures to oral formulations. The majority of all exposures to zolmitriptan (95%) were at doses equal to or greater than 2.5 mg.

Table 6: Subject Exposures in the Clinical Pharmacology Studies

Route	No. of unique subjects	No. of Expo-sures	Initial Dose of Zolmitriptan (mg)							
			PBO	<2.5	2.5	>2.5-<5	5.0	>5-10	>10-20	>20-50
Oral	316	869	136	22	100	5	183	419	116	24
I.V.	32	64		30	12	22				
I.N.	24	60	12		32		8	20		
Total	**316**	**993**	**148**	**52**	**144**	**27**	**191**	**439**	**116**	**24**

I.V.=intravenous, I.N.=intranasal, PBO=placebo

Sponsor generated Table 7 summarizes the extent of exposures in the nine patient treatment studies. A total of 4,759 (non-unique) patients were administered zolmitriptan as a either a single dose per attack (2,912 single dose administrations) or as two doses per attack (1,847 two dose administrations). Table 8 is a sponsor generated table which summarizes, according to initial dose, the extent of exposure to zolmitriptan in the patient treatment studies.

Table 7: Exposures in the Patient Treatment Studies

Study Category	Study Characteristics	No. of Patients exposed to zolmi-triptan	No. of Patients treated with:		Total No. of Attacks Treated with zolmi-triptan	Total No. of Attacks Treated with:	
			One Dose	Two Doses		One Dose	Two Doses
Patient Studies for the Treatment of Migraine							
Placebo-controlled	Inpt, optional 2nd dose	79	55	24	79	55	24
	Outpt, single dose	1,550	1,550	N/A	1,550	1,550	N/A
	Outpt, optional 2nd dose	1,004	789	215	1,004	789	215
Uncontrolled	Outpt, multiple attack, opt 2nd dose	2,058	463	1,595	31,579	17,140	14,439
	Inpt, single dose	38	38	N/A	38	38	N/A
Sub-Total		4,729	2,895	1,834	34,250	19,572	14,678
Patient Study for the Prevention of Migraine Headache							
Placebo-controlled	Outpt, two attack, opt 2nd dose	30	17	13	46	33	13
All Patient Studies							
Total		4,759	2,912	1,847	34,296	19,605	14,691

Table 8: Patient Exposures by Initial Dose of Zolmitriptan in Patient Studies

Study Category	Study Characteristics	PBO	Initial Dose of Zolmitriptan							
			1	2.5	5	10	15	20	25	Total
Patient Studies for the Treatment of Migraine										
Placebo Controlled	Inpt, opt 2nd dose	5	22		21	15			21	79
	Outpt, single dose	256		200	711	214	215	210		1,550
	Outpt, opt 2nd dose	140	141	298	280	285				1,004
Uncontrolled	Outpt, mult attack, opt 2nd dose				2,058					2,058
	Inpt, single dose					38			18	56
Sub-Total		401	163	498	3,070	552	215	210	39	4,747
Patient Studies for the Acute Prevention of Migraine										
Placebo-Controlled	Outpt, two attack, opt 2nd dose	4						46		46
All Patient Studies										
Total		405	163	498	3,070	552	215	256	39	4,793

PBO=placebo

Patients received zolmitriptan over the dose range of 1 to 25 mg. The majority of exposures were 5 mg (3,070 or 4,793; 64%) as this was the dose used in the long-term, multiple attack study (015). As in the Clinical Pharmacology studies, the preponderance (97%) of the zolmitriptan initial dose administrations (4,584 out of 4,747 administrations) in the placebo controlled and uncontrolled patient treatment studies were at doses of 2.5 mg and higher.

5.2 Secondary Data Sources

None.

5.2.1 Other Studies

No other studies outside the IND are included in the NDA.

5.2.2 Post-marketing Experience

Zolmitriptan is not marketed outside the U.S. No post-marketing experience is available.

5.3 Adequacy of Human Experience

This NDA contains data which document exposure to zolmitriptan in over 4,000 volunteers and patients. Subject exposures encompass an age range of 12-76 years, with a female to male ratio of 85:15 for migraine patients. Long term exposures to zolmitriptan include 669 patients who treated more than 2 migraine attacks per month over 6 months, and 137 of these were treated for approximately one year. These exposures satisfy International Conference on Harmonization (ICH) exposure guidelines for long-term safety evaluation of anti-migraine compounds.

6. Human Pharmacokinetics

Zolmitriptan is well absorbed following oral administration (64%). Individual plasma concentration time profiles sometimes showed multiple peaks. Along with intersubject C_{max} variability, this resulted in wide range of T_{max} (0.5 to 6 h). On average, 75% of C_{max} is achieved within 1 h of dosing and levels were sustained for several hours post-dose. Food has no effect on absorption.

The absolute bioavailability of zolmitriptan is 39-40% for the two proposed marketing doses of 2.5 mg and 5.0 mg. Zolmitriptan is 23-27% plasma protein bound and protein binding is independent of plasma concentration over the range 10-200 ng/mL. There was no drug-related material accumulation in red blood cells. The major PK parameters are summarized in Table 9.

Table 9: Human Pharmacokinetic Profile, Zolmitriptan

C_{max}	3.8 ng/mL	(2.5 mg p.o.)
	3.9 7.8 ng/mL	(5 mg p.o.)
T_{max}	2.25 h	(2.5 mg p.o.)
	3 h	(5 mg p.o.)
AUC	20.7 ng/mL/h	(2.5 mg p.o.)
	20.8 46.4 ng/mL/h	(5 mg p.o.)
$T_{1/2}$	2.5 - 3 h	
CL (i.v.)	10 mL/min/kg	(1/3 = renal)
Vz	2.4 L/kg	
protein binding	25%	

Zolmitriptan is metabolized to three major forms. N-desmethyl zolmitriptan is metabolically active at $5HT_{1D}$ and is 2-6 times more potent as the parent compound. Plasma concentrations are approximately half of parent compound and the plasma profile mirrored that of the parent. The two other forms, n-oxide and the indole acetic acid forms are metabolically inactive. About 8% of zolmitriptan is excreted in the kidney with a renal clearance higher than the GFR suggesting active renal tubular secretion. The N-desmethyl metabolite has a CL_R approximating the GFR.

The $T_{1/2}$ of zolmitriptan and its metabolites is 2.5-3 hours and is independent of dose.

The pharmacokinetics of zolmitriptan were linear following single doses from 2.5-10 mg. Across studies, zolmitriptan PK were proportional from doses of 2.5-50 mg and zolmitriptan PK were proportional following multiple doses of 5 and 10 mg.