CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20768

STATISTICAL REVIEW(S)

RETURN

Statistical Review and Evaluation

NDA:	20-768	JUN 16 1997
Sponsor:	Zeneca Pharmaceuticals	
Drug:	ZOMIG (zolmitriptan)	
Indication:	Acute Migraine	
Statistical Reviewer:	Qing Liu, Ph.D.	

1. Review Summary

This NDA submission consists of five randomized placebo controlled studies for the treatment of migraine headache. The primary efficacy measure for Studies 008, 042, 017 and 006 is headache response at 2 hours, while that for Study 18 is complete response and headache response at 2 hours post dose is a secondary endpoint. This submission considers headache response at 2 hours the primary endpoint.

Based on this review, each of the five studies has succeeded in achieving its own objectives and the evidence in supporting the efficacy of ZOMIG over placebo is overwhelming.

2. Major Review Issues

2.1 Pivotal Studies

Since Study 18 is well controlled and contains relevant efficacy information, it should be included among the other four trials in the assessments of aggregate evidence of efficacy for ZOMIG versus placebo. The sponsor only considers Studies 008, 042, 017 and 006 as *pivotal*, while Study 18 as *supportive*. However, it is not clear whether such classification is due to the fact that its primary endpoint was not headache response at 2 hours and it also contained an active control arm, or *because the results of sponsor's analyses were statistically not significant.*

2.2 Primary Endpoint

Headache response to migraine drugs is evaluated on a four-point pain scale: Severe, Moderate, Mild or None. The primary endpoint is headache response at 2 hours post-dose. For a patient with moderate or severe baseline headache pain to be considered as a responder, the headache response has to be classified as MILD or NONE.

By definition, patients with severe baseline headache need a higher degree of improvement of **two** points (Severe to Mild or None) than that of an **one**-point improvement (Moderate to Mild or None) for those with moderate baseline headache. Because the definition of headache response is on an *absolute* scale, the criterion for patients with severe headache is more *stringent* than that for patients with moderate headache.

Because of the *double standard* nature of the endpoint, results based on an analysis that *ignores the baseline severity* are difficult to interpret:

1) The overall estimates of the response rates are *less informative and potentially misleading,*
2) Test procedures that do not adjust for the baseline severity can be *insensitive* to certain departures from the null, and
3) Results of prognostic factor analysis of baseline severity are *meaningless.*

These points will be elaborated in later sections of the review.

2.3 Prognostic value of Baseline Severity

The sponsor has demonstrated that the response rates for patients with severe baseline headache are consistently lower than those with moderate baseline headache with the exception of Study 018. Because of this result, it seems that the treatment with ZOMIG is less effective for patients with severe baseline headache than those with only moderate baseline headache. This result, however, is very likely a *statistical artifact* rather than a medically meaningful finding, due to the double standard nature of the endpoint. A more sensible measure of efficacy should be based on a *relative* scale, looking at, say, improvement from baseline; and reevaluate the prognostic value baseline within this context (see Section 7).

3. Randomization, Dosing and Analysis Population

Study	Population	PBO	1mg	2.5mg	5mg	10mg	15mg	20mg	25mg
006	Randomized	20	22	----	21	----	----	----	21
	All-Treated	20	22	----	21	----	----	----	21
	Protocol-Prefered	20	22	----	21	----	----	----	21
008	Randomized	126	----	----	265	262	270	258	----
	All-Treated	99	----	----	213	214	215	210	----
	Protocol-Prefered	88	----	----	179	191	194	188	----

017	Randomized All-Treated Protocol-Prefered	154 140 121	158 141 125	317 298 260	313 280 245	316 285 248	---- ---- ----	---- ---- ----	---- ---- ----
018	Randomized All-Treated Protocol-Prefered	74 56 47	---- ---- ----	---- ---- ----	614 498 420	---- ---- ----	---- ---- ----	---- ---- ----	---- ---- ----
042	Randomized All-Treated Protocol-Prefered	108 101 92	---- ---- ----	219 200 178	---- ---- ----	---- ---- ----	---- ---- ----	---- ---- ----	---- ---- ----

Note that the *All-Treated population* refers to all randomized patients known to have taken any study drug and the *Protocol-Prefered* population refers to patients in the All-Treated population who adhered to protocol requirements. Because the All-Treated population is essentially the Intent-to-Treat population, *the remaining sections of this review shall be based on the All-Treated population unless stated otherwise.*

4. Summary of Response Rates

Tables below summarize the overall response rates as well as response rates for different baseline severities. It will be shown that response rates based on baseline severities are more informative than the overall response rates.

4.1 Headache Response at 2 hours Post-dose for Protocol-Prefered Population

4.1.1 Study 006

Dose	Moderate Baseline			Severe Baseline			Overall RR
	SS*	NR**	RR***	SS	NR	RR	
Placebo	16	3	**19%**	4	0	**0%**	**15%**
1mg	17	6	**35%**	5	0	**0%**	**27%**
5mg	16	11	**69%**	5	2	**40%**	**62%**
25mg	13	12	**92%**	8	5	**63%**	**81%**

* SS --- Sample Size; ** NR --- Number of Responses; *** RR = NR/SS, the observed Response Rate.

4.1.2 Study 008

Dose	Moderate Baseline			Severe Baseline			Overall RR
	SS	NR	RR	SS	NR	RR	
Placebo	45	10	22%	43	7	16%	21%
5mg	99	70	71%	80	48	60%	61%
10mg	115	91	79%	76	45	59%	67%
15mg	111	83	75%	83	51	61%	67%
20mg	117	96	82%	71	49	69%	74%

4.1.3 Study 017

Dose	Moderate Baseline			Severe Baseline			Overall RR
	SS	NR	RR	SS	NR	RR	
Placebo	102	39	38%	19	2	11%	32%
1mg	92	52	57%	33	14	42%	50%
2.5mg	203	141	69%	57	28	49%	63%
5mg	186	131	70%	59	32	54%	65%
10mg	193	145	75%	55	22	40%	66%

4.1.4 Study 018

Dose	Moderate Baseline			Severe Baseline			Overall RR
	SS	NR	RR	SS	NR	RR	
Placebo	29	12	41%	18	10	56%	44%
5mg	240	169	70%	180	86	48%	59%

4.1.5 Study 042

Dose	Moderate Baseline			Severe Baseline			Overall RR
	SS	NR	RR	SS	NR	RR	
Placebo	73	29	40%	19	4	21%	36%
2.5mg	133	89	67%	45	21	47%	62%

4.2 Complete Headache Response for All-Treated Population

Dose	Moderate Baseline			Severe Baseline			Overall RR
	SS*	NCR**	CRR***	SS	NCR	CRR	
Placebo	37	10	27%	18	8	44%	38%
5mg	262	133	51%	208	60	29%	41%

* SS --- Sample Size; ** NCR --- Number of Complete Responses; *** CRR --- Complete Response Rate

4.3 Comments

There are two points to make.

- Except for Study 018, the response rates for patients with severe baseline headache are consistently lower than those with moderate baseline headache.

  This by no means indicates that treatments with ZOMIG is less effective for patients with severe baseline headache than those with moderate headache. A more sensible way would be looking at the improvement from baseline (see Section 7).

- Treatment effects are *remarkably consistent* across studies for patients with moderate baseline than those with severe baseline.

  Doses 2.5mg and 5mg are effective (statistically significant) dose levels that were studied in at least two trials. For dose 2.5mg, the response rates are 69% and 67% for Studies 017 and 042 for patients with moderate baseline, and the respective rates are 49% and 47% for patients with severe baseline headache. For dose 5mg, the response rates are 69%, 71%, 70% and 70% for Studies 006, 008, 017 and 018 for patients with moderate headache, while the corresponding response rates are 40%, 60%, 54% and 48% for patients with severe baseline headaches.

5. Summary of Statistical Significance by Fisher's Exact Test

5.1 Methods

Analyses of the following are based on the one-sided Fisher's exact test for the alternative that ZOMIG is more effective than placebo with respect to headache response at 2 hours post-dose against the null that the two treatments are equally ineffective. The test procedure is valid in the sense of protecting the false positive rate under the null, and a significant p-value can be interpreted as evidence against the null in favor of the alternative.

5.2 Headache response rates at 2 hours post-dose

5.2.1 Study 006

Dose	Sample Size	Number of Responses	Response Rate	P-values		
				Placebo*	1mg**	5mg***
Placebo	20	3	15%	----	----	----
1mg	22	6	27%	0.2789	----	----
5mg	21	13	62%	**0.0025**	**0.0233**	----
25mg	21	17	81%	**<0.0001**	**0.0005**	0.1529

* comparisons of higher doses to placebo; ** comparisons of higher doses to 1mg;
*** comparisons of higher dose to 5mg. *Similar notations are used for the remaining studies.*

5.2.2 Study 008

Dose	Sample Size	Number of Responses	Response Rate	P-values			
				Placebo	5mg	10mg	15mg
Placebo	99	21	21%	----	----	----	----
5mg	213	130	61%	**<0.0001**	----	----	----
10mg	213	143	67%	**<0.0001**	0.1128	----	----
15mg	215	143	67%	**<0.0001**	0.1404	0.3138	----
20mg	209	154	74%	**<0.0001**	**0.0038**	0.0858	0.0659

5.2.3 Study 017

Dose	Sample Size	Number of Responses	Response Rate	P-values			
				Placebo	1mg	2.5mg	5mg
Placebo	139	44	32%	----	----	----	----
1mg	140	70	50%	0.0023	----	----	----
2.5mg	298	189	63%	<0.0001	0.0053	----	----
5mg	280	182	65%	<0.0001	0.0022	0.3790	----
10mg	282	185	66%	<0.0001	0.0015	0.3223	0.4755

5.2.4 Study 018

Dose	Sample Size	Number of Responses	Response Rate	P-value
Placebo	55	24	44%	----
5mg	491	288	59%	0.0237

5.2.5 Study 042

Dose	Sample Size	Number of Responses	Response Rate	P-value
Placebo	99	36	36%	----
2.5mg	197	122	62%	<0.0001

5.3 Complete Headache Response for Study 018

Dose	Sample Size	Number of Complete Responses	Complete Response Rate	P-value
Placebo	55	18	38%	----
5mg	470	193	41%	0.4190

5.4 Comments

- The efficacy of ZOMIG at doses of 2.5mg and above as measured by the headache response rates at 2 hours post-dose has been consistently demonstrated and the evidence is beyond any doubt.

- For headache response at 2 hours, the effect of ZOMIG 5mg for Study 018 is less significant (0.0237) as compared to other studies with the same dose (0.0025 for Study 006, <0.0001 for Studies 008 and 017). As seen from Section 4.1.4 the primary reason is not that ZOMIG is less effective but that the response rate for patients on placebo with severe baseline headache is exceptionally high. *It should be cautioned those this by no means implies that the treatment is less effective, as compared to placebo, for patients with moderate baseline headache.* A more sensible analysis would *stratify* patients according to the baseline severity and *do not assume homogeneity* of treatment effects.

- According to the Fisher's exact test, Study 018 has failed to demonstrate the effectiveness of ZOMIG 5mg with respect to complete headache response. However, the same reasons and caution apply here.

6. Summary of Statistical Significance using a Stratified Analysis

In the previous section, it is seen that the treatment effect is less or not significant according to the Fisher's exact test for Study 018. Thus, the focus here is to reanalyze Study 018 using a stratified analysis to demonstrate the deficiencies of the Fisher's exact test.

6.1 Methods

To take into consideration the double standard feature of the headache response, a more natural way of data analysis is to stratify according to patients baseline severity and make treatment comparisons among patients with the same baseline severity. A popular procedure is the Mantel-Haenszel test for stratified analysis. Because the statistical model underlying the Mantel-Haenszel test assumes that the odds ratio are homogeneous, the procedure loses statistical power if in fact the odds ratios are heterogeneous. *In the context of this review, the criteria for headache response are different for different baseline severities, and therefore, the assumption of common odds ratio would seem rather illogical.* For this review, an order-restricted test is considered (Agresti and Coull, 1996; Liu, 1997), which unlike the Mantel-Haenszel test does not require that odds ratios be constant across different strata.

6.2 Headache Response at 2 hours Post-dose for Protocol-Prefered Population

Dose	Moderate Baseline			Severe Baseline			P-value
	SS	NR	RR	SS	NR	RR	
Placebo	29	12	41%	18	10	56%	----
5mg	240	169	70%	180	86	48%	0.004

6.3 Complete Headache Response

Dose	Moderate Baseline			Severe Baseline			P-value
	SS	NCR	CRR	SS	NCR	CRR	
Placebo	37	10	27%	18	8	44%	----
5mg	262	133	51%	208	60	29%	0.0112

6.4 Comments

- The results of the order-restricted test clearly demonstrate that *ZOMIG is effective in terms of both the headache response rate at 2 hours and complete response rate for treatment of migraine headache*, and the bulk of the statistical evidence arises from comparisons of ZOMIG with placebo for patients with moderate baseline headache.

  Thus, the overall study results should be considered as positive.

- For patients with severe baseline headache, the response rate of ZOMIG is observed to be lower than that of placebo. *This does not indicate that ZOMIG is less effective, but rather the placebo response rate is exceptionally high relative to observations from other studies for some unknown reason.*

7. Prognostic Factor Analysis of Baseline Headache Severity

7.1 Definition and Methods

This section considers headache improvement from baseline as the measure of headache conditions 2 hours post-dose. Specifically, the headache improvement is defined as

follows: 0 for no improvement. 1 for improvement by 1 degree. i.e. from SEVERE to MODERATE or MODERATE to MILD. and 2 for improvement by at least 2 degrees. i.e. from SEVERE to MILD or NO PAIN or from MODERATE to NO PAIN.

Two studies will be used to analyze the data. Study 008 will be used for data exploration while Study 017 will be used for confirmation. Because Study 008 was designed to explore the upper end of the dose-response curve and the headache response rates are very similar among different doses, the ZOMIG group in the following analysis consists of combined dose levels 5mg, 10mg, 15mg and 20mg. While for Study 017, the object was to explore the lower end of the dose-response curve and because dose level 1mg has not been consistently shown significantly different from placebo, the Placebo group consists of those treated with placebo and 1mg ZOMIG and the ZOMIG group consists of combined dose levels 2.5mg, 5 mg and 10mg.

The proportional odds model is used to analyze the significance of the baseline severity as well as the treatment with ZOMIG on headache improvements.

7.2 Results of Study 008

Treatment	Headache Improvement from Baseline					
	Moderate Baseline			Severe Baseline		
	0	1	2	0	1	2
Placebo	37 75.51%	11 22.45%	1 2.04%	30 60%	11 22%	9 18%
ZOMIG	124 25.36%	142 29.04%	223 45.60%	73 20.22%	83 22.99%	205 56.79%

The p-value for testing efficacy of ZOMIG is 0.0001 and that for the interaction of treatment by baseline severity is 0.0022. *The significant interaction effect is due to large differences in placebo response rates between strata, not treatment response rates.*

7.3 Results of Study 017

Treatment	Headache Improvement from Baseline					
	Moderate Baseline			Severe Baseline		
	0	1	2	0	1	2
Placebo	120 55.56%	72 33.33%	24 11.11%	23 36.51%	22 34.92%	18 28.57%
ZOMIG	191 29.25%	236 36.14%	226 34.61%	59 28.92%	51 25%	94 46.08%

The p-value for testing efficacy of ZOMIG is 0.0001 and that for the interaction of treatment by baseline severity is 0.0427.

7.4 Comments

Both studies have consistently demonstrated that

- baseline headache severity is prognostic with respect to headache improvement *only for untreated patients*; that patients with severe baseline are likely to have 2 degrees of improvement; and

- treatment with ZOMIG significantly increases patients chances for headache improvement and the improvements are *comparable* among patients with different headache severity, i.e. baseline headache severity is ***not prognostic*** for patients treated with an effective dose of ZOMIG.

8. Conclusions

- *ZOMIG 2.5mg and above provides an effective treatment for acute migraine headache. This result is consistently demonstrated in five well-controlled studies and the evidence is beyond any doubt.*

- *This review has clearly demonstrated that the headache response is a **misleading** measurement of treatment outcome. It is strongly recommended that the study results be based on headache improvement from baseline. Furthermore, this should be primary endpoint for other migraine NDAs.*

9. Reference

Agresti, A., and Coull, B. A. (1996). Order-Restricted Tests of Conditional Independence for Stratified Ix2 Tables. Biometrics, accepted.

Liu, Q. (1997). Order-Restricted Inference for 2x2 Tables with Heterogeneous Odds Ratios. In preparation.

This review contains 13 pages.

6/5/97

Qing Liu, Ph.D.
Mathematical Statistician

Concur:

6/5/97

Todd Sahlroot, Ph.D.
Team Leader

6/16/97

George Chi, Ph.D.
Director, Division of Biometrics I

cc: Archival NDA 20,768; ZOMIG (Zolmitriptan)

HFD-120/Division File
HFD-120/Dr. Leber
HFD-120/Dr. Levin
HFD-120/Ms. Chen
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Liu
HFD-710/Chron.

RECEIVED OCT 0 2 1997

Statistical Review and Evaluation

Addendum

OCT 2[nd] 1997

NDA:	20-768
Sponsor:	Zeneca Pharmaceuticals
Drug:	ZOMIG (zolmitriptan)
Indication:	Acute Migraine
Statistical Reviewer:	Qing Liu, Ph.D.

---

1. Introduction

This review is an addendum to the Statistical Review and Evaluation for NDA 20-768 for Zolmitriptan for acute migraine dated June 16, 1997. The issue to be addressed here; as requested by Dr. Levin (HFD-120 Team Leader), is the effectiveness of the second dose of Zolmitriptan for patients who either had persistent headache or had recurrence.

The sponsor designed one study, Study 17, to allow evaluation of the efficacy of the second dose. In order to make the comparison valid, patients were randomized to treatment sequences such that they either took a second dose of the initial treatment or placebo. The primary endpoint for the second dose was the response rate 2 hours after the second dose. The tables in this addendum were extracted from Dr. Levin's review pertaining to the efficacy of a second dose.

2. Efficacy of the Second Dose

The efficacy of the second dose can be addressed in various ways, involving different subgroups of patients who received the second dose. In all the comparisons, patients who took rescue prior to the 2 hour endpoint assessment need to excluded. Because of the small number of patients receiving rescue medication, the exclusion of these patients has no impact on the validity of the statisitcal findings. The following subgroups of patients were examined.

1) All patients who received a second dose (Table 1).

2) Patients with severe or moderate baseline headache prior to receiving a second dose (Table 2).

3) Patients with persistent headache 4 hours following the initial dose (Table 3).

4) Patients who were responders 4 hours following the initial dose with headache recurrence including mild pain.

5) Patients who were responders 4 hours following the initial dose with headache recurrence excluding mild pain.

All the analyses are stratified according to the initial dose, since it affects the response rates of the second dose. The Mantel-Haenszel test was used for p-value computation. The StatXact package was used for computing exact 2-sided p-values. Because of the stratification, those who received placebo initially do not contribute to the analysis. Note that this approach is different from that of the sponsor in that 1) active treatment groups were combined and 2) patients who were on placebo initially were included in the sponsor's analysis.

Table 1: Response Rates of Patients Receiving a Second Dose

Second Randomization	Placebo (N = 61)	1 mg (N = 68)	2.5 mg (N = 125)	5 mg (N = 111)	10 mg (N = 84)
Placebo	19/61=31%	15/36=42%	27/60=45%	31/58=53%	25/41=61%
Original Dose		16/32=50%	37/65=57%	33/53=62%	30/43=70%

p-value = 0.0384.

Table 2: Second Dose Response Rates of Patients with Severe or Moderate Baseline

Second Randomization	Placebo (N = 52)	1 mg (N = 56)	2.5 mg (N = 90)	5 mg (N = 78)	10 mg (N = 62)
Placebo	11/52=21%	10/31=32%	14/44=31%	18/42=43%	17/30=57%
Original Dose		11/25=44%	23/46=50%	17/36=47%	22/32=69%

p-value = 0.0541.

Table 3: Second Dose Response Rates of Patients who were non-Responders

Second Randomization	1 mg (N = 39)	2.5 mg (N = 46)	5 mg (N = 45)	10 mg (N = 30)
Placebo	5/20=25%	8/22=36%	10/23=43%	7/14=50%
Original Dose	8/19=42%	11/24=46%	9/22%=41%	9/16=56%

p-value = 0.4232.

Table 4: Second Dose Response Rates of Patients with Recurrence, Including Mild Pain

Second Randomization	1 mg (N = 29)	2.5 mg (N = 79)	5 mg (N = 66)	10 mg (N = 54)
Placebo	10/16=63%	19/38=50%	21/35=60%	18/27=67%
Original Dose	8/13=62%	26/41=63%	24/31=77%	21/27=78%

p-value = 0.0708.

Table 5: Second Dose Response Rates of Patients with Recurrence, Excluding Mild Pain

Second Randomization	1 mg (N = 18)	2.5 mg (N = 47)	5 mg (N = 37)	10 mg (N = 35)
Placebo	5/11=45%	8/25=32%	11/22=50%	11/17=65%
Original Dose	4/7=57%	12/22=55%	8/15=53%	14/18=78%

p-value = 0.1179.

3. Summary

The results of data analysis did not yield statistical significance at 0.05 level for some tests. However, every analysis showed a positive trend which is indicative of efficacy for the second dose, and the lack of statistical significance is very likely the result of inadequate sample size.

This review contains 4 pages.

10/2/97

Qing Liu, Ph.D.
Mathematical Statistician

Concur:

10/2/97

Todd Sahlroot, Ph.D.
Team Leader

10/2/97

George Chi, Ph.D.
Director, Division of Biometrics I

cc: Archival NDA 20,768; ZOMIG (Zolmitriptan)

HFD-120/Division File
HFD-120/Dr. Leber
HFD-120/Dr. Levin
HFD-120/Ms. Chen
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Liu
HFD-710/Chron.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20768

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 10 1997

SEP 1 0 1997

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Zolmitriptan (Zomig®)
2.5 and 5 mg Tablets

Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850-5437

NDA 20-768 **Submission Dates:**
November 26, 1996
February 03, 1997
March 24, 1997
June 05, 1997
July 14, 1997
August 13, 1997

IND 45-147 **October 28, 1996**

Reviewer: **Vijay K. Tammara, Ph. D.**

Indication: Migraine
Classification: 1S
Type of Submission: Original--New Molecular Entity

= =

Zolmitriptan (commonly referred to as 311C90) is a selective 5-hydroxytryptamine$_{1D}$ receptor agonist. The mechanism of action is presumably by acting both centrally and peripherally at 5-HT$_{1D}$ receptors to produce cranial vessel constriction and inhibition of neuropeptide release and thereby exerting its therapeutic effect. The recommended dose is 2.5 mg. If symptoms persist or return within 24 hours, a second dose can be taken. If a second dose is required, it should not be taken within 2 hours of the initial dose. If patient does not achieve satisfactory relief with 2.5 mg doses, subsequent migraine attacks can be treated with 5 mg doses.

RECOMMENDATION:

This submission (NDA 20-768) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable for meeting the Office's requirements, provided that the sponsor incorporates all the labeling changes. The biowaiver request for the 5 mg tablet can be granted based on results of dissolution profiles. The sponsor is requested to adopt the dissolution methodology and specification as outlined in **Comment 4**. Please forward **Comments 1-4, Labeling Comments** and this **Recommendation** to the sponsor.

Table of Contents

	Page #
Synopsis	1
Recommendation	1
Introduction	6
Summary of Human BA/PK/PD	7
Comments	20

APPENDIX I: Individual Study Summary

I. BIOAVAILABILITY

1. A Study to Determine the Absolute Bioavailability of Oral Tablet Formulations of 2.5 mg and 5 mg 311C90 in Healthy Male and Female Volunteers (Study 045 (BLVS/96/0017).

2. A Comparison of the Rate and Extent of Absorption of 311C90 from a Solution and a Tablet in Healthy Male Volunteers (Study 028 (BLVS/95/0022).

3. A Bioequivalence Study to Compare the Bioavailability of Final Production Process 2.5 mg and 5 mg Tablets of 311C90 with the Clinical Trial Material 2.5 and 5 mg Tablets (Study 025 (BLVS/96/0015).

4. A Trial to Assess the Bioequivalence of Zeneca Manufactured and GlaxoWellcome Manufactured Zolmitriptan (Zomig™) 2.5 mg Tablets in Healthy Male and Female Volunteers (Study 091 (311CIL/0091).

5. Bio-waiver Request: Rationale and Justification

6. A Study to Determine if the Pharmacokinetics of Single Oral Doses of 2.5 mg, 5 mg and 10 mg 311C90 are Dose Proportional and to Examine the Effect of Food on the Pharmacokinetics of a Single Oral Dose of 5 mg (Study 044 (BLVS/96/0016).

II. PHARMACOKINETICS/ ADME

7. A Study of the Disposition of 311C90 in Man Following the Administration of ^{14}C–311C90 to Healthy Volunteers (study 011 (BLVS/95/0017).

8. A Study of Protein Binding of C–311C90 in Human Plasma (BDDM/92/0004/01).

9. A Study to Investigate the Metabolism of 311C90 In Vitro Using Hepatic Sub-Cellular Fractions (BDRR/94/0025).

10. The Effect of 311C90 on the Cytochrome P450 Metabolism of Probe Substrates In Vitro in Human Liver Microsomes (BDRR/96/0011).

11. Investigation of the Potential of 311C90 to Interact With the Monoamine Oxidase System in Human Liver Mitochondria (BDRR/96/0012).

III. DOSE PROPORTIONALITY STUDY

A Study to Determine if the Pharmacokinetics of Single Oral Doses of 2.5 mg, 5 mg and 10 mg 311C90 are Dose Proportional and to Examine the Effect of Food on the Pharmacokinetics of a Single Oral Dose of 5 mg (Study 044 (BLVS/96/0016).

12. A Double–blind, Placebo Controlled Dose–escalation Study of the Tolerability, Pharmacokinetics and Pharmacodynamic Effects of 311C90 in Healthy Male Volunteers (Study 001 (BLVS/93/0023).

IV. MULTIPLE DOSE STUDY

13. Report of a Placebo Controlled Study to Examine the Tolerability to Multiple Doses of 5 mg and 10 mg 311C90 and to Compare the Single and Multiple Dose Pharmacokinetics of a 10 mg Dose in Healthy Volunteers (Study 014 (BLVS/95/0030).

V. SPECIAL POPULATIONS

14. Report of a Double–Blind, Placebo Controlled, Randomized, Balanced, 4–Limb, Crossover Study to Compare the Tolerability, Pharmacokinetics and Pharmacodynamic Effects of 311C90 in Healthy Young and Elderly Volunteers (Study 012 (BLVS/95/0029).

A Bioequivalence Study to Compare the Bioavailability of Final Production Process 2.5 mg and 5 mg Tablets of 311C90 with the Clinical Trial Material 2.5 and 5 mg Tablets (Study 025 (BLVS/96/0015).

15. Report of a Study to Compare the Pharmacokinetics of a Single Oral Dose of 10 mg of 311C90 in Healthy Volunteers and Renal Failure Subjects not Requiring Dialysis (Study 024: (BLVS/96/0012).

16. A Trial to Compare the Pharmacokinetics of and Tolerability to A Single, Oral, 10 mg dose of 311C90 in Healthy Volunteers and Patients with Liver Disease (Study 030 (311CIL/0030).

17. 311C90 Phase I Clinical Study – Dose Ranging Study in Japanese Subjects (Study 311C–1 (NW1).

18. A Safety, Pharmacokinetic, and Pharmacodynamic Assessment of Single Doses of 311C90 in Volunteers with Mild to Moderate Hypertension Compared to Normotensive Healthy Volunteers (Study 013 (RM1996/00157/00).

VI. DRUG INTERACTIONS

19. A Study of the Pharmacokinetic and Pharmacodynamic Interactions between the 5HT1D Agonist 311C90 and Ergotamine in Healthy Volunteers (Study 010 (BLVS/95/0016).

20. Report of a Placebo–Controlled Study to Examine the Effect of Concomitantly Administered Propranolol on the Pharmacokinetics of and Tolerability to the Antimigraine Compound 311C90 (Study 021 (BLVS/96/0006).

21. A Randomized, Crossover Study of the Potential Interactions between 311C90, Paracetamol and Metoclopramide (Study 033 (BLVS/95/0037).

22. A Double–Blind Placebo–Controlled Study to Investigate the Effect of Multiple Doses of Fluoxetine on the Pharmacokinetics and Pharmacodynamics of a Single 10 mg 311C90 Dose in Healthy Female and Male Volunteers (Study 035 (RM1996/00158/00).

23. Report of an Open Study to Examine the Effect of Concomitantly Administered Selegiline or Moclobemide (Selective Monoamine Oxidase Inhibitors) on the Pharmacokinetics of the Novel Antimigraine Compound 311C90 (Study 038 (BLVS/96/0007).

24. Report of a Study to Investigate Whether Multiple Doses of Dihydroergotamine Affect the Pharmacokinetics and Pharmacodynamics of a Single Oral Dose of 10 mg 311C90 in Healthy Volunteers (Study 039 (BLVS/96/0014).

25. Oral Contraceptives: Retrospective Analysis.

VII. PHARMACOKINETICS IN PATIENTS

26. An Open Study to Investigate the Pharmacokinetics and Tolerability of Oral 311C90 and to Obtain a Preliminary Indication of Efficacy in Patients with Migraine (Study 007 (BLVS/94/0036).

APPENDIX A - OCPB LABELING COMMENTS/SPONSOR'S LABELING

APPENDIX I - STUDY REPORTS

APPENDIX II- ANALYTICAL METHODOLOGY

APPENDIX III- DRUG FORMULATION

APPENDIX IV- IN VITRO DISSOLUTION

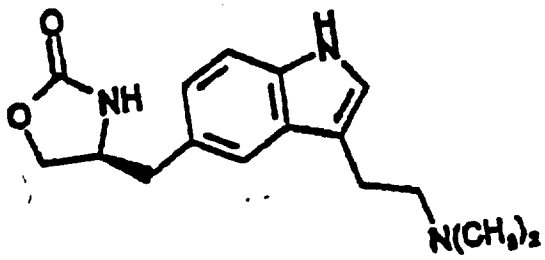
APPENDIX V - LIST OF STUDIES THAT WERE NOT REVIEWED

(The above Appendices are available in the Office of Clinical Pharmacology and Biopharmaceutics archive files. A total of 32 studies were submitted, of which 7 were found to be either repetitive and pilot in nature or involved a dosage form not relevant to this submission, and hence only 25 studies were reviewed).

ZOMIGI™ NDA 20-768
Vijay Tammara

INTRODUCTION:

Zolmitriptan is a selective 5-hydroxytryptamine$_{1D}$ receptor agonist. It is chemically known as (S)-4-[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Its molecular formula is $C_{16}H_{21}N_3O_2$ and the molecular weight is 287.36. Zolmitriptan is a white to almost white powder and is readily soluble in water (1.3 mg/mL) and 0.1 N HCL (33 mg/mL). Its structural formula is as follows:



DOSAGE FORMS AND ADMINISTRATION

Most of the pharmacokinetic studies were carried out after oral administration of Zolmitriptan film coated tablets. Tablets manufactured at different sites were used in the clinical studies.

In the study involving ^{14}C-311C90 administration, the active ingredient was administered in capsule form. In the bioequivalence studies, the 2.5 and 5 mg final production dosage forms (Dartford, UK) were compared to 2.5 and 5 mg clinical trial tablets (Dartford, UK) used in the pivotal Phase 3 studies. Lastly, the final 2.5 mg to be marketed dosage form (IPR, Puerto Rico) was compared to 2.5 mg final production dosage form (Dartford, UK).

MANUFACTURER: Manufactured by IPR Pharmaceuticals Inc., Puerto Rico.

SUMMARY OF HUMAN BIOAVAILABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS

I. BIOAVAILABILITY:

A. Absolute Bioavailability: In an open, balanced, randomized, 4-period crossover study in 20 healthy volunteers (10 M and 10 F), the mean absolute bioavailability of Zolmitriptan following oral administration of 2.5 and 5 mg tablets and 0.925-2.95 mg IV infusion was found to be 40% (CV = 30%) in both males and females (Study 045 (BLVS/96/0017).

Plasma concentration time profiles for 311C90 and active metabolite 183C91 exhibited multiple (two) peaks following oral administration, resulting in a wide range of Tmax values (0.5-6.0 hrs). However, no such multiple peaks were observed following IV administration. Thus, the second peak of 311C90 and 183C91 is likely to be an absorption phenomenon following oral administration, rather than a result of enterohepatic recycling, as the second peak is not observed following IV administration.

Following oral administration of 2.5 and 5 mg tablets, the mean Cmax and AUC values observed in females were 4.1 ± 1.8 ng/mL, 9.7 ± 4.3 ng/mL, 23.1 ± 9.8 ng*hr/mL, and 60.2 ± 26.8 ng*hr/mL, respectively; whereas in males the mean Cmax and AUC values observed were 3.5 ± 1.2 ng/mL, 5.9 ± 2.0 ng/mL, 18.4 ± 5.4 ng*hr/mL, and 32.7 ± 10.1 ng*hr/mL, respectively.

Relative Bioavailability: In an open, randomized, two-period, single dose, cross over study involving seven healthy male volunteers, the mean relative bioavailability following oral administration of 10 mg film coated tablets relative to an oral solution was 96% (CV = 24%) (Study 028 (BLVS/95/0022). Further, it was observed that the rate of absorption was slower from film-coated tablets than solution (Tmax 2.6 ± 1.9 vs 1.3 ± 0.6 hrs), but this was not statistically significant.

B: Bioequivalence:

In the bioequivalence study (Study 025 (BLVS/96/0015), the 2.5 and 5 mg tablets (Treatment A and C, respectively) used in the pivotal clinical trials (Clinical Trial Material (CTM); Study 017 and 042) were compared with the final production 2.5 and 5 mg tablets (Treatment B and D, respectively). This study was conducted as a single-dose, randomized, open-label, four-period cross over study in 20 healthy subjects (10M, 10F). Using 2.5 mg CTM i.e., treatment A as the

reference treatment for statistical comparisons, treatment B (2.5 mg TBM) was found to be bioequivalent in terms of log transformed extent of absorption, i.e., $AUC_{0-\infty}$ (90% C.I. = 92-110% and 92-111%); C_{max} (90% C.I. = 84-107% and 84-107%) for both Zolmitriptan (311C90) and its desmethyl metabolite (183C91), respectively. Similarly, using treatment C as the reference treatment (5.0 mg CTM) for statistical comparisons, treatment D (5.0 mg TBM) was found to be bioequivalent in terms of log transformed extent of absorption, i.e., $AUC_{0-\infty}$ (90% C.I. = 95-114% and 94-113%); C_{max} (90% C.I. = 95-121% and 94-120%) for both Zolmitriptan (311C90) and its desmethyl metabolite (183C91), respectively. No statistically significant difference in Tmax was observed.

In another bioequivalence study (Study 091 (311CIL/0091), the final production 2.5 mg tablets (GlaxoWellcome (GW) Formulation, UK) were compared with the proposed to be marketed 2.5 mg tablets (Zeneca Formulation, Puerto Rico; IPR). This study was conducted as a randomized, 5 mg single-dose, open-label, two-period cross over study in 20 healthy subjects (10M, 10F). Using GW formulation as the reference treatment for statistical comparisons, IPR formulation was found to be bioequivalent in terms of log transformed extent of absorption, i.e., $AUC_{0-\infty}$ (90% C.I. = 90-110% and 92-103); C_{max} (90% C.I. = 81-109% and 86-104%) for both Zolmitriptan (311C90) and its desmethyl metabolite (183C91), respectively. No statistically significant difference in Tmax was observed.

C: Waiver Request: The sponsor intends to change the site of manufacture of 5 mg strength tablets from Dartford, UK to IPR, Puerto Rico and did not perform bioequivalence study for this dosage strength. The 5 mg tablet is compositionally proportional to the 2.5 mg tablet; Zolmitriptan exhibits linear pharmacokinetics over the proposed dosage regimen; and the drug appears to be highly soluble and low permeability. Based on the above facts and similar dissolution profiles of 5 mg tablets manufactured at Dartford, UK and IPR, Puerto Rico, a biowaiver could be granted.

D: Interaction with Food:

This was a randomized, open-label, balanced, single oral dose, 4-period cross over study in which a 5 mg Zolmitriptan tablet was administered to 12 healthy subjects (6M, 6F) after an overnight fast and after a standardized breakfast (non-FDA meal consisting of 2 pieces of white bread, one fried egg, 50 g each of fried bacon and sausage, 100 mL homogenized milk, 25 g corn flakes, 100 mL orange juice, 15 g butter and 30 g marmalade (total of 967 Kcal) Study 044 (BLVS/96/0016), to evaluate the effect of food on the pharmacokinetics of

zolmitriptan. It was observed that in the presence of food AUC and Cmax of 311C90 decreased by about 15% and Tmax increased by one-half hour, whereas desmethyl metabolite (183C91) AUC and Cmax were similar between fed and fasted states. These changes were not statistically significant. Thus, it can be concluded that food has no affect on the pharmacokinetics of Zolmitriptan.

II. PHARMACOKINETICS:

A. Absorption:

Radiolabeled Zolmitriptan is absorbed with about 65% of the radioactive oral dose recovered in the urine over a period of 7 days (Study 011 (BLVS/95/0017)). Following oral administration, average peak plasma concentration occurs in about 0.5 to 6 hours (Studies 011, 025, 091, and 045).

B. Distribution:

In Vivo

The extent and degree of Zolmitriptan's distribution within various body compartments has not been systematically studied in humans. Following oral administration of 2.5 and 5 mg tablets in 20 healthy subjects (10M, 10F; Study 045 (BLVS/96/0017), mean apparent steady-state volume of distribution (Vz/F) was found to be 7 L/Kg (CV = 17%).

In Vitro Protein Binding:

In human serum, about 25% of Zolmitriptan is bound to plasma proteins over the *in vitro* concentration range of 10-1000 ng/mL and binding does not appear to be saturable (BDDM/92/0004/01).

C. Metabolism :

In Vivo

Zolmitriptan is highly metabolized mainly to 3 major metabolites: N-desmethylated zolmitriptan (183C91), N-oxide analog (1652W92), and indole acetic acid (2161W92), and a number of minor metabolites (Study 011 (BLVS/95/0017)). Of these metabolites, only 183C91 has been reported to be active as a 5-HT_{1D} agonist and the other two metabolites are inactive. The

active metabolite (183C91) was found to be present in plasma at concentrations about 60% that of Zolmitriptan. The metabolism of Zolmitriptan is mostly hepatic. Following a single 25 mg oral dose of ^{14}C-Zolmitriptan in 6 healthy subjects (5M, 1F) an average of 92% of total radioactivity was recovered in urine (65%) and feces (30%) over 7 days, while 8% remained unrecovered. About 8% of the Zolmitriptan dose was recovered in the urine as unchanged drug and metabolites accounted for about 42% (i.e., metabolites indoleacetic acid, N-oxide and N-desmethyl accounted for about 31%, 7, and 4%, respectively). Other minor metabolites accounted for about 15% of the dose recovered in urine. In feces, Zolmitriptan accounted for most of the labeled dose recovered, indicating that at least this amount of drug remains unabsorbed.

Comparison of Zolmitriptan pharmacokinetics based on specific HPLC assay for Zolmitriptan and its metabolite plasma concentrations and total plasma radioactivity indicated that known analytes accounted for 86% of ^{14}C-measured in plasma, of which the unchanged drug was about 21%(CV = 18%). The metabolites accounted for the remainder 65% of total radioactivity in plasma, of which the major component was inactive indole acetic acid metabolite 2161W92 which accounted for 40% of total radioactivity in plasma, while the active desmethyl metabolite (183C91) accounted for about 14%. In general, the shape of the plasma concentration vs time profiles for metabolites are the same shape as zolmitriptan.

In Vitro Metabolism of Zolmitriptan

The *in vitro* metabolism of 311C90 was investigated (Study BDRR/94/0025) using a variety of hepatic tissues from both rat and human sources and expressed human enzymes. However, the concentrations of zolmitriptan used in these experiments were too high (100 μM) and were irrelevant because physiologically relevant concentrations will be less than 0.1 μM.

Further studies with human microsomes over a range of substrate concentrations (1-100 μM) with a single characterized human liver known to have elevated levels of most CYP450 isozymes (including 3A4 and 2D6) showed some conversion of zolmitriptan (1 and 10 μM) to 183C91 (desmethyl metabolite) in the presence of NADPH.

Effect of Zolmitriptan on the CYP450 Metabolism of Probe Substrates:

In an *in vitro* study (Study BDRR/96/0011) the effect of zolmitriptan on the *in vitro* metabolism of CYP450 probe substrates has been investigated in pooled

male and female human liver microsomes. The study showed inhibition of bufuralol and phenacetin metabolism, probe substrates for CYP 2D6 and CYP1A2, respectively, only at very high concentrations of zolmitriptan (100-500 μM and 20-1000 μM, respectively). Further, zolmitriptan was found to have no effect on the metabolism of any other CYP450 probe substrates studies (probes for 2A6, 2C8/9/10/19, 2E1, and 3A). Therefore, it is unlikely that zolmitriptan at therapeutic concentrations, would affect the CYP 450 metabolism of any coadministered drug.

Effect of Zolmitriptan on MAO Enzyme Systems:

In another *in vitro* study (Study BDRR/96/0012), the inhibitory effect of zolmitriptan on monoamine oxidase (MAO) enzyme systems has been investigated using specific probe substrates for MAO-A (^{3}H-5HT) and MAO-B (^{14}C-Benzylamine). The study results indicated that there was no significant inhibition of either ^{3}H-5HT or ^{14}C-Benzylamine over a concentration range of 2.5-250 μM (too high a concentration) of zolmitriptan, indicating no inhibitory effect of zolmitriptan on either MAO-A or MAO-B.

D. Elimination:

The mean elimination half-life of zolmitriptan was found to be 3 hrs across all doses. In general, the half-life of all major metabolites were similar to that ~~to~~ of zolmitriptan. The mean apparent plasma clearance (Cl/F) of Zolmitriptan was found to be 31.5 mL/min/kg (CV = 43%; Study 045).

III. DOSE PROPORTIONALITY:

In a randomized, open-label, balanced, single oral dose, 4-period cross over study, 2.5, 5, and 10 mg Zolmitriptan film coated tablets were administered to 12 healthy subjects (6M, 6F) after an overnight fast to determine whether the pharmacokinetics of zolmitriptan is linear and dose proportional (Study 044 (BLVS/96/0016). It was observed that dose-normalized AUC and Cmax were similar and not statistically significantly different between doses. Thus, it can be concluded that zolmitriptan exhibited linear pharmacokinetics following single oral doses in the range of 2.5 - 10 mg.

In another single dose study the pharmacokinetics of zolmitriptan was evaluated following escalating doses of 1 (n = 4), 3(n = 5), 6 (n = 9), 12 (n = 9), 25 (n = 9), and 50 mg (n = 7) . This study is a double-blind, randomized, dose-escalating, placebo controlled study in healthy volunteers (Study 001- (BLVS/93/0023).

Pharmacokinetic parameters were not calculated for dose levels 1 and 3 mg, since the analytical method was not sensitive enough to detect plasma concentrations beyond 4 hours. It was observed that AUC and Cmax for zolmitriptan and active desmethyl metabolite increased in a dose proportional manner from 6 mg to 50 mg. Thus, it can be concluded that across studies, zolmitriptan pharmacokinetics were linear from doses of 2.5 to 50 mg.

In a multiple dose study involving 12 healthy subjects (10M, 2F), dose proportionality at two dose levels of 5 and 10 mg was evaluated (Study 014 (BLVS/95/0030). The results of this study indicated that mean AUC and Cmax values following multiple doses of 5 and 10 mg were proportional to the dose. Thus, it can be concluded that Zolmitriptan displays linear kinetics over the multiple dose range of 5 to 10 mg.

IV. MULTIPLE DOSE STUDY

In a multiple dose study involving 12 healthy subjects (10M, 2F), pharmacokinetics of zolmitriptan were evaluated following multiple doses of 5 and 10 mg (Study 014 (BLVS/95/0030)). This study was a randomized, cross-over study, with three double-blind, multiple dose periods and an open period with a single dose in 12 healthy subjects. Subjects received a single 10 mg dose of zolmitriptan and multiple doses (q6H for 5 doses) of 5 and 10 mg zolmitriptan and placebo. The results of the study showed that there is no significant accumulation following multiple doses.

V. SPECIAL POPULATIONS

Age

In a single dose (placebo, 5, 10, and 15 mg), double-blind, placebo-controlled, randomized, balanced, 4-limb, crossover study, the pharmacokinetics of zolmitriptan was investigated following oral administration in 12 young (mean age: 29 ± 6 yrs; 6F, 6M) and 12 elderly (mean age: 69 ± 3 yrs; 6F, 6M) subjects (Study 012 (BLVS/95/0029)). All subjects received 4 treatments at weekly intervals. From the results, it was observed that there was no overall difference in the mean pharmacokinetic parameters of 311C90 and 183C91 in the elderly compared to young.

However, it was observed that mean Cmax and $AUC_{0-\infty}$ of 311C90 increased 35% and 50%, respectively, in elderly male than young male, but were comparable for the metabolite 183C91. These parameters are comparable between young and elderly women for both zolmitriptan and its active metabolite.

Gender

The sponsor did not conduct a formal pharmacokinetic study to examine gender related differences in the pharmacokinetics of zolmitriptan. However, a retrospective analysis of pharmacokinetic data was performed by this reviewer to identify gender related differences in the pharmacokinetics of zolmitriptan.

In one study, the pharmacokinetics of zolmitriptan was investigated in 10 healthy female subjects (mean body weight = 63 ± 8 Kg) and 10 healthy male subjects (mean body weight = 73 ± 12 Kg) following a single oral administration of 2.5 and 5 mg tablets (Study 025). On an average, females had 37% and 25% higher AUC and Cmax values for 311C90 and 183C91 than males (after taking into account the correction for body weight).

In another study (Study 012), where volunteers were given 5, 10, and 15 mg single oral doses, young females were found to have two-fold higher AUC and Cmax values for zolmitriptan than young males, whereas elderly females have comparable AUC and Cmax values compared to elderly males.

In a third study involving a single oral dose of placebo, 5, 10, and 20 mg of zolmitriptan, the pharmacokinetics was investigated in 17 normotensive (9F, 8M) and 16 mild to moderate hypertensive (8F, 8M) patients (Study 013 (RM1996/00157/00)). It was observed that mean Cmax and $AUC_{0-\infty}$ of 311C90 were two-fold higher in females than males.

Thus, gender does appear to affect the pharmacokinetics of zolmitriptan.

Renal Impairment

In a single-dose (10 mg), open label study involving 15 renal patients (creatine clearance (Cl_{cr}) ≤ 5 - 50 mL/min/1.73m^2) and 15 age and sex matched healthy subjects (Cl_{cr} ≥ 70 mL/min/1.73m^2), pharmacokinetics of zolmitriptan was investigated (Study 024: (BLVS/96/0012)). The reviewer reclassified renal impairment into three groups, instead of two originally provided by the sponsor, and these groups are as follows:

Normal (Cl_{cr} ≥ 70 mL/min/1.73m^2; (n = 15);
Moderate (Cl_{cr} ≥ 25-50 mL/min/1.73m^2; (n = 6)
Severe (Cl_{cr} ≥ 5 - 25 mL/min/1.73m^2; (n = 9)

Moderate vs Normal: No significant change in mean C_{max} and $AUC_{0-\infty}$ was

observed for 311C90, but renal clearance decreased by 71% (50 mL/min vs 174 mL/min) in moderately renally impaired group in comparison to normal group. However, a modest increase was observed for mean C_{max} and $AUC_{0-\infty}$ of metabolite 183C91. Inter-subject variability for these pharmacokinetic parameters was observed to be comparable between the two groups.

Severe vs Normal: Mean C_{max} and $AUC_{0-\infty}$ increased by 27% (19.3 vs 24.5 ng/mL) and 60% (105.1 vs 167 ng*hr/mL), respectively, for 311C90 in severely renally impaired group in comparison to normal group. An increase in $AUC_{0-\infty}$ resulted in a corresponding decrease in Clearance (CL/F) by 25% (1895 vs 1423 mL/min). Renal clearance was also observed to be decreased by 85% (174 vs 27 mL/min) in severely renally impaired group in comparison to normal group. Mean C_{max} and $AUC_{0-\infty}$ of metabolite 183C91 increased by 14% (11.3 vs 9.9 ng/mL) and 48% (88 vs 60 ng*hr/mL), respectively. Inter-subject variability for these pharmacokinetic parameters was observed to be comparable between the two groups. Thus, it can be concluded that renal impairment does not affect the pharmacokinetics of zolmitriptan significantly.

Hepatic Impairment

In a single-dose (10 mg), non-randomized, open label, parallel group, multi center study involving 10 patients with moderate liver disease, 16 patients with severe liver disease, and 10 healthy subjects matched for age, sex, weight, and smoking-habit, to the patients with moderate liver disease, the pharmacokinetics of zolmitriptan was investigated (Study 030 (311CIL/0030). From the results it was observed that mean Cmax of 311C90 increased by 50% (21 vs 31 and 32 ng/mL) in both hepatically impaired patient groups. Further, mean $AUC_{0-\infty}$ and half-life were increased by two-fold and three fold (117 vs 212 and 384 ng*hr/mL) and by 57% and 157% (4.6 vs 7.2 and 11.8 hrs), in moderately and severely hepatically impaired patients, respectively; Tmax increased by two-fold in severely hepatically impaired. This could be attributed to reduced metabolism of zolmitriptan resulting in higher peak plasma concentrations, increased exposure, and prolonged half-life in patients with liver disease. Consequently, there was a decrease in exposure to the principal metabolite of zolmitriptan as evidenced by a corresponding decrease in Cmax and $AUC_{0-\infty}$ of 183C91 in the hepatically impaired in comparison to age and sex-matched healthy subjects.

Based on the above results, it can be concluded that the liver disease has a pronounced effect on the pharmacokinetics of zolmitriptan and hence the dose of zolmitriptan may need to be reduced in subjects with liver disease. However, these results are based on a single 10 mg dose of zolmitriptan, but at 2.5 mg

dose, recommeded for therapeutic use, the differences in the pharmacokinetics of zolmitriptan in subjects with liver disease may not be that significant.

Race

The sponsor did not conduct a formal pharmacokinetic study to examine the affect of race on the pharmacokinetics of Zolmitriptan. However, retrospective analysis of pharmacokinetic data across studies conducted in Japanese ((Study 311C–1 (NW1)) and Caucasians (Study 045 (BLVS/96/0017) was performed by this reviewer to identify the affect of race on the pharmacokinetics of zolmitriptan.

Zolmitriptan follows linear kinetics in Japanese subjects also. Comparison of the pharmacokinetics between Japanese and Caucasians at 2.5 and 5 mg doses, revealed no significant differences.

Hypertensive Patients

In a single dose (placebo, 5, 10, and 20 mg), double-blind, placebo-controlled, randomized, four-period, four-treatment, crossover study, the pharmacokinetics of zolmitriptan was investigated following oral administration in 17 normotensive (9F, 8M) and 16 mild to moderate hypertensive (8F, 8M) patients (Study 013 (RM1996/00157/00)). Normotensive patients had a supine systolic blood pressure ≥90 mm Hg and ≤140 mm Hg and a diastolic blood pressure ≥50 mm Hg and ≤90 mm Hg. Hypertensive patients had a supine systolic blood pressure ≥130 mm Hg and ≤180 mm Hg and a diastolic blood pressure ≥80 mm Hg and ≤110 mm Hg with diuretic therapy. All patients received 4 treatments at weekly intervals. From the results, it was observed that there was no difference in mean Cmax and Tmax for both 311C90 and 183C91, while $AUC_{0-\infty}$ of 311C90 increased by an average 30% at highest dose (20 mg) in mild to moderate hypertensive patients in comparison to normotensive patients. Further, it was observed that mean Cmax and $AUC_{0-\infty}$ of 311C90 were two-fold higher in females than males. Systolic and diastolic blood pressure increased in a dose-dependent manner following administration of 311C90 in normotensive and hypertensive patients.

VI. DRUG INTERACTIONS

Ergotamine: In a double-blind, randomized, balanced, open label, single dose, four way cross-over drug interaction study between zolmitriptan and ergotamine involving 12 healthy volunteers, the pharmacokinetics of zolmitriptan was

investigated alone and in combination with ergotamine. Volunteers received a single 20 mg oral tablet of 311C90, 2 mg ergotamine and 200 mg caffeine (2 Cafergot tablets), the two drugs in combination, and placebo (Study 010 (BLVS/95/0016). It was observed that the concurrent administration of zolmitriptan and ergotamine/caffeine resulted in decreased plasma levels of 311C90 and 183C91 as reflected by decreases in Cmax (13 and 19%), Tmax (30% and 13%) and $AUC_{0-\infty}$ (13 and 7%), respectively, but this may not have clinical significance. Further, no significant changes in the pressor effects were observed in combination. Therefore, it can be concluded that ergotamine/caffeine does not significantly affect the pharmacokinetics of zolmitriptan.

Propranolol: In a double-blind, randomized, placebo controlled, two way cross-over drug interaction study between zolmitriptan and propranolol involving 14 healthy volunteers (6F, 8M), the pharmacokinetics of zolmitriptan was investigated alone and in combination with propranolol. Volunteers received 160 mg propranolol (long acting) or matching placebo daily for 7 days (blinded), and on the last day of each period volunteers received a single 10 mg tablet of 311C90 (unblinded) (Study 021 (BLVS/96/0006). The propranolol dosing occasion was completed by 14 and placebo occasion by 12 volunteers. It was observed that seven days of dosing of propranolol with a single 10 mg dose of 311C90 on the last day was associated with an increase in mean 311C90 Cmax and $AUC_{0-\infty}$ by 40% (22 vs 16 ng/mL) and 65% (166 vs 101 ng*hr/mL), respectively, and a corresponding reduction in CL/f by 40% (1790 vs 1100 mL/min), when compared with zolmitriptan alone. There were associated reductions in the Cmax and $AUC_{0-\infty}$ of metabolite 183C91 of 30% (6.6 vs 4.6 ng/mL) and 15% (45 vs 39 ng*hr/mL), respectively. Tmax of 311C90 and its metabolites were not affected. Further, propranolol did not affect the blood pressure increase associated with zolmitriptan.

Therefore, it can be concluded that Propranolol does affect the pharmacokinetics of zolmitriptan.

Paracetamol and Metoclopramide: In a randomized, open cross over drug interaction study between zolmitriptan, paracetamol, and metoclopramide involving 15 healthy volunteers (6F, 9M), the pharmacokinetics of zolmitriptan was investigated alone, and in combination with paracetamol, metoclopramide, and paracetamol and metoclopramide. Volunteers received a single 10 mg 311C90 alone, 1 g paracetamol alone, 10 mg 311C90 plus 1 g paracetamol, 10 mg 311C90 plus 10 mg metoclopramide, and 10 mg 311C90 plus 1g paracetamol plus 10 mg metoclopramide. From the results, it was noted that

there was no evidence of a statistical interaction between paracetamol and metoclopramide on 311C90 pharmacokinetics, individually or together. There were no significant effects of either paracetamol or metoclopramide on any of the 183C91 pharmacokinetic parameters. It was also observed that in the presence of 311C90, paracetamol Tmax occurred an hour later. Metoclopramide was not assayed in this study. Further, neither paracetamol nor metoclopramide had any affect on the blood pressure increase associated with zolmitriptan.

Therefore, it can be concluded that neither Paracetamol nor metoclopramide affect the pharmacokinetics of zolmitriptan.

Selegiline or Moclobemide: In a randomized, open, three way cross over drug interaction study between zolmitriptan, selegiline, and/or moclobemide involving 12 healthy volunteers (6F, 6M), the pharmacokinetics of zolmitriptan was investigated alone and in combination with selegiline or moclobemide. Volunteers received either selegiline (10mg once daily), moclobemide (150 mg twice daily) or nothing for 7 days, with a 10 mg dose of 311C90 given on the last day with the last dose of selegiline or penultimate dose of moclobemide. From the results, it was observed that selegiline had no effect on the pharmacokinetics of 311C90 and its metabolites. In contrast, concomitant administration of moclobemide with 311C90, resulted in increase in mean Cmax and $AUC_{0-\infty}$ values of 311C90 by 24% (17 vs 21 ng/mL) and 28% (107 vs 137 ng*hr/mL) with a corresponding decrease in CL/F. A three-fold increase in Cmax and $AUC_{0-\infty}$ of 183C91 was observed in the presence of moclobemide. Further, neither selegiline nor moclobemide had any affect on the blood pressure increase associated with zolmitriptan.

Dihydroergotamine: In a double blind, randomized, balanced, open, two period cross over drug interaction study between zolmitriptan and dihydroergotamine involving 12 healthy volunteers (6F, 6M), the pharmacokinetics of zolmitriptan was investigated alone and in combination with dihydroergotamine (BLVS/96/0014). Volunteers received either dihydroergotamine (5 mg bid) or placebo for 10 days, with a single 10 mg oral dose of 311C90 given on the last day with the last dose of dihydroergotamine or placebo. From the results, it was observed that dihydroergotamine had no effect on the pharmacokinetics of 311C90 and its metabolites. Further, dihydroergotamine had no affect on the blood pressure increase associated with zolmitriptan.

Therefore, it can be concluded that dihydroergotamine does not affect the pharmacokinetics of zolmitriptan.

Fluoxetine: In a double blind, randomized, placebo-controlled, balanced, open, two period crossover drug interaction study between zolmitriptan and fluoxetine involving 20 healthy volunteers (15F, 5M), the pharmacokinetics of zolmitriptan was investigated alone and in combination with fluoxetine (RM1996/00158/00). Volunteers received either fluoxetine (20 mg once daily) or matching placebo for 28 days, with a single 10 mg oral dose of 311C90 given on the last day with the last dose of fluoxetine or placebo. Sixteen volunteers completed the study (both dosing periods). From the results, it was observed that fluoxetine had no effect on the pharmacokinetics of 311C90 and its metabolites. Further, fluoxetine had no affect on the blood pressure increase associated with zolmitriptan.

Oral Contraceptives: The sponsor did not conduct a formal pharmacokinetic drug interaction study to examine the affect of oral contraceptives on the pharmacokinetics of Zolmitriptan. However, a retrospective analysis of pharmacokinetic data across studies was performed by this reviewer to identify the affect of oral contraceptives on the pharmacokinetics of zolmitriptan (Table 2). It was observed that mean plasma concentrations of zolmitriptan were generally higher in females taking oral contraceptives compared to those not taking oral contraceptives; mean Cmax and AUC were found to be higher by 30% and 50%, respectively. The time to reach peak concentration was delayed at least by half an hour in females taking oral contraceptives.

These observations were further confirmed by the sponsor's retrospective analysis performed upon the request of this reviewer and involving a total of 141 females, 57 taking oral contraceptives and 84 not taking oral contraceptives.

VII. PHARMACOKINETICS IN PATIENTS

Pharmacokinetics of Zolmitriptan in patients during migraine and migraine free period (BLVS/94/0036): In an open, non-randomized, two-period study in 20 hospitalized patients (16F, 4M), the pharmacokinetics of zolmitriptan following a single 10 mg oral dose was investigated during a moderate to severe migraine attack and again on a subsequent occasion after being migraine free for at least 48 hours. Plasma samples were collected up to 4 hours during and outside a migraine attack. From the results, it was observed that the mean Cmax and AUC_{0-4} were lower by 25% (10 vs 13 ng/mL) and 40% (22 vs 35 ng*hr/mL), respectively, during a migraine attack than during a migraine free period. Further, it was observed that the time to reach peak concentrations was delayed by half-an hour (3.4 vs 2.7 hrs) in migraine patients compared to migraine free

period. The Tmax for the active metabolite 183C91 was also delayed by half-an hour.

APPENDIX II: ANALYTICAL METHODOLOGY

APPENDIX III: DRUG FORMULATION

Zolmitriptan tablet formulations used in the clinical trials/pharmacokinetic studies, and the proposed to be marketed formulation are similar qualitatively in inactive ingredients except for povidone being removed from the TBM formulation. Further, the method of manufacture is wet granulation vs direct compression.

APPENDIX IV: IN VITRO DISSOLUTION

The sponsor provided *in vitro* dissolution information on film-coated Zolmitriptan tablets (bio-batch; the to-be-marketed dosage form) at 3 time points (15, 30, and 45 minutes) in From the data it was observed that dissolution for the film-coated tablets is rapid in (greater than dissolved in 15 minutes).

The sponsor was requested to provide dissolution profiles, both graphical as well as tabular data of 12 individual tablets and mean data. Based on the results provided, following dissolution methodology and specification is recommended for Zomig 2.5 and 5 mg film-coated tablets:

Medium:
Apparatus:
Specification:

Comments To Be Sent To The Firm:

1) The sponsor is requested to calculate mean pharmacokinetic parameters in addition to geometric means and to construct mean plasma concentration time profiles instead of median plasma concentration time profiles in their future studies.

2) In future food effect studies, the sponsor is requested to use the FDA recommended high fat meal.

3) The sponsor is requested to construct confidence intervals for future drug-drug interaction studies in addition to p-values.

4) The sponsor is requested to adopt the following dissolution methodology and specification for Zomig 2.5 and 5 mg film-coated tablets:

Medium:	500 mL 0.1 N HCl at 37 ± 0.5°C
Apparatus:	USP Apparatus II (paddle) at 50 rpm
Specification:	Not less than 80% in 15 minutes

****

09/10/97

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

First Draft Prepared on June 4, 1997
First draft initialed by Dr. Hossain on June 25, 1997
Second Draft prepared on July 3,1997
Second Draft Initialed by Dr. Baweja on August 11, 1997
Third Draft Prepared on August 21, 1997
Inter-Division CP/B Briefing Date: September 4, 1997
Attendees: Henry Malinowski, Mehul Mehta, Randy Levin, Armando Oliva, Heimann Martha, Mei-Ling Chen, Raymond Miller, Shiew-Mei Huang, Janice Jenkins, Raman Baweja, and Vijay Tammara.

FT Initialed by R. Baweja, Ph. D. ---------- R. Baweja 9/10/97
CC: NDA 20,768 (orig.), HFD-120, HFD-860 (Tammara, Baweja, Malinowski), CDR (Barbara Murphy).