CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Frovatriptan Succinate Monohydrate (MIGUARD™) 2.5 mg tablets
Vanguard Medica Limited, Chancellor Court, Surrey Research Park, Surrey, UK.
Submission Date: February 22, 2000.
NDA 21-006
Reviewers: Iftekhar Mahmood, Ph. D. and Maria Sunzel, Ph.D.
Indication: Migraine Treatment

Addendum to the original NDA 21-006

The Sponsor has submitted the **detailed dissolution** data of their product Frovatriptan (MIGUARD™). The Sponsor's proposed Dissolution Method and Specifications for frovatriptan tablets are as follows:

Dosage Form:	Tablet
Strengths:	2.5 mg
Apparatus:	USP Apparatus II (Paddle)
Medium:	900 mL phosphate buffer (pH = 5.5)
Speed:	50 rpm.
Sampling Times:	10, 20, and 30 minutes

Sponsor's proposed specification of Q = ——— minutes.

More than — drug is dissolved in — minutes. Looking at the stability batches, it appears that there may be systematic error in dissolution profiles of 12 month stability data (Appendix I) as compared to 18 and 24 months. Furthermore, the data indicate that the dissolution profiles of frovatriptan are almost similar in phosphate buffer (pH = 5.5) and in 0.1N HCl.

Due to high solubility of frovatriptan, the Sponsor's proposed specifications of Q = ——— minutes may not be appropriate as this specification may not detect a faulty batch.

Comment:

The FDA's proposed dissolution specifications are as follows:

Apparatus:	USP Apparatus II (Paddle)
Medium:	900 mL phosphate buffer (pH = 5.5)
Speed:	50 rpm.

FDA's proposed specification of Q = _____ minutes

Recommendation:

The Sponsor is requested to adopt the dissolution method and specifications as outlined in comment above.

Iftekhar Mahmood, Ph.D. /S/ 3/22/2000

Maria Sunzel, Ph.D. /S/ 3/22/00

RD/FT initialed by Raman Baweja, Ph.D. /S/ - 3/22/00

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-006, HFD-120, HFD-860 (Mahmood, Sunzel, Baweja, Mehta), HFD-340 (Viswanathan), CDR-Biopharm (for Drug-Files) and FOI (HFD-19) files.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX I

QT525 VML 251 2.5mg Tablets Batch number SB001 packed in —— blisters stored at 25°/60% RH

Study Number QT525

Product Batch Number SB001

Start Date January 13, 1998

Container —— blisters

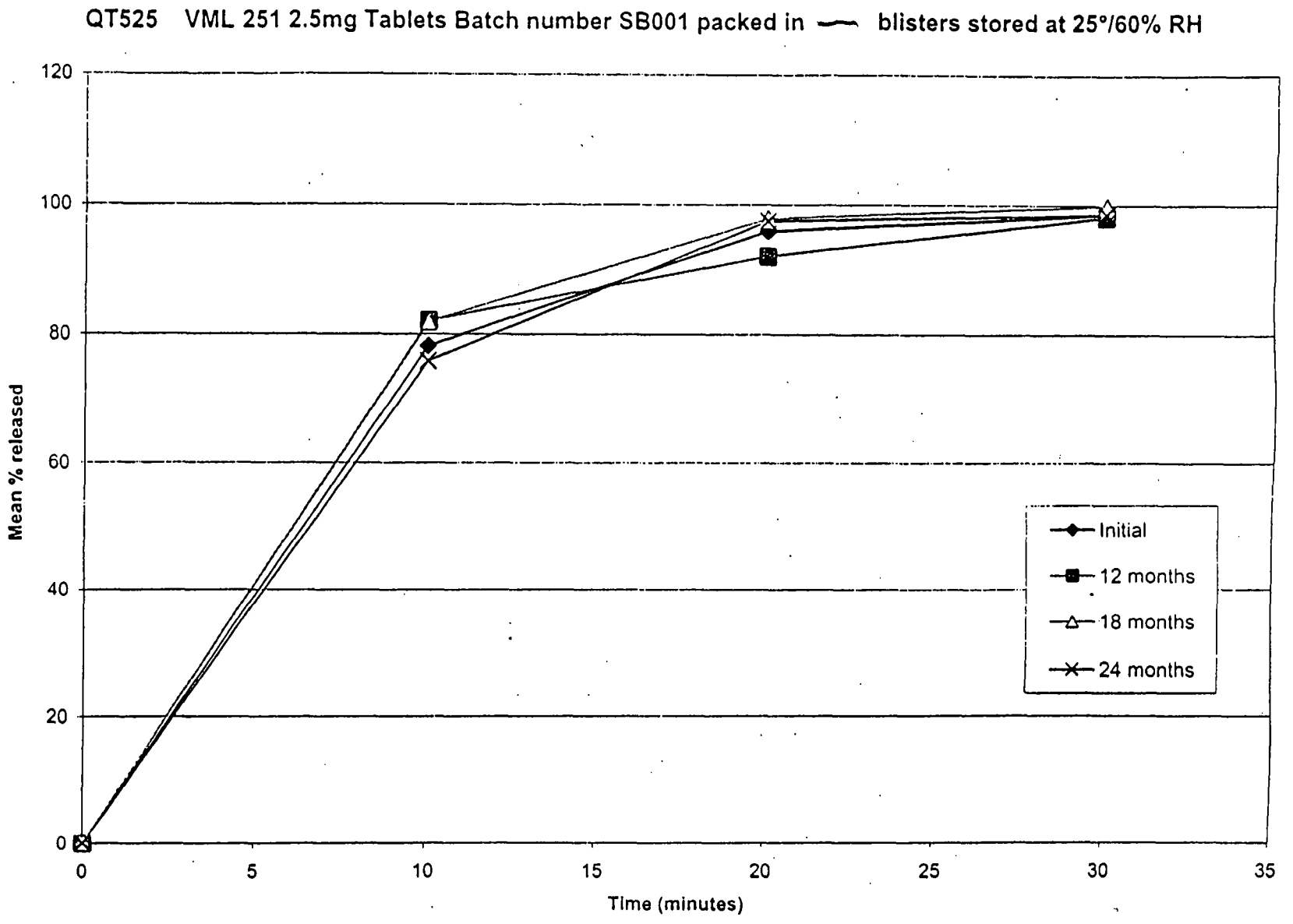
Storage conditions 25°/60% RH

Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							78.2	1.5
	20							96.0	1.9
	30							98.6	2.6

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							82.0	1.6
	20							92.0	2.2
	30							98.2	2.0

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							77.8	3.8
	20							99.3	2.3
	30							102.6	1.9

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	
Time point (mins)	0							0.0	0.0
	10							87.0	2.3
	20							96.9	1.9
	30							97.5	1.9


QT525 VML 251 2.5mg Tablets Batch number SB001 packed in — blisters stored at 25°/60% RH
Mean % released
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Time (minutes)
Initial
12 months
18 months
24 months

QT530 VML 251 2.5mg Tablets Batch number SB002 packed in ___ blisters stored at 25°/60% RH

Study Number QT530

Product Batch Number SB002

Start Date January 13, 1998

Container ___ blisters

Storage conditions 25°/60% RH

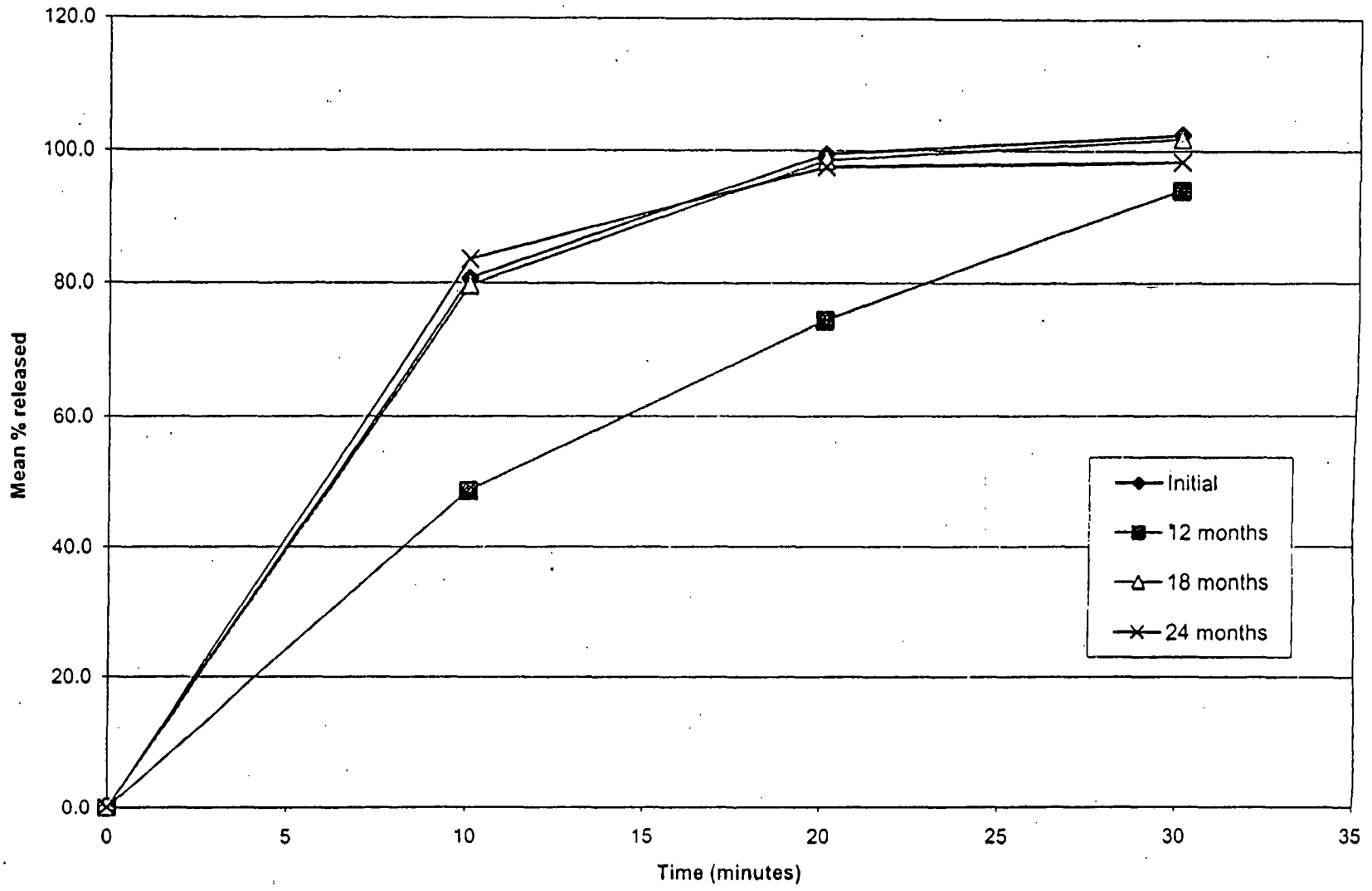
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							80.7	2.8
	20							99.4	1.4
	30							102.4	1.5

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							48.7	4.2
	20							74.4	9.6
	30							94.0	5.6

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							79.7	3.8
	20							98.4	2.1
	30							101.8	1.0

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	
Time point (mins)	0							0.0	0.0
	10							83.5	3.7
	20							97.5	0.7
	30							98.3	0.9

QT530 VML 251 2.5mg Tablets Batch number SB002 packed in → blisters stored at 25°/60% RH



QT519 VML 251 2.5mg Tablets Batch number SB004 packed in blisters stored at 25°/60% RH

Study Number QT519

Product Batch Number SB004

Start Date January 13, 1998

Container blisters

Storage conditions 25°/60% RH

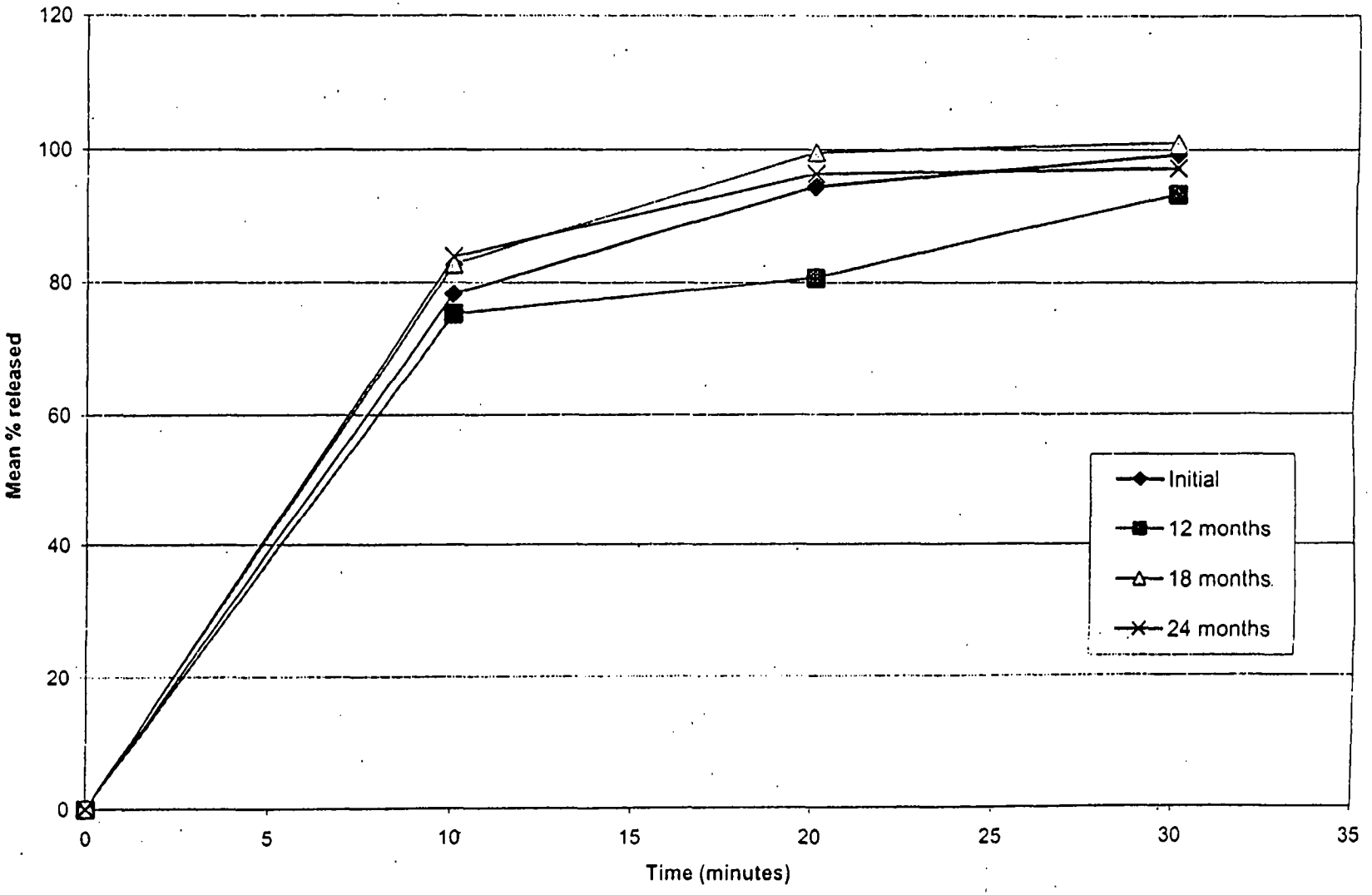
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							78.3	4.0
	20							94.4	2.5
	30							99.3	2.2

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							75.3	5.9
	20							80.7	7.0
	30							93.3	3.6

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							82.7	6.5
	20							99.5	2.1
	30							101.0	1.5

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							83.8	5.6
	20							96.3	1.8
	30							97.2	2.2

QT519 VML 251 2.5mg Tablets Batch number SB004 packed in ⟷ blisters stored at 25°/60% RH



QT493 VML 251 2.5mg Tablets Batch number SB005 packed in —— stored at 25°/60% RH

Study Number QT493

Product Batch Number SB005

Start Date December 2, 1997

Container ——

Storage conditions 25°/60% RH

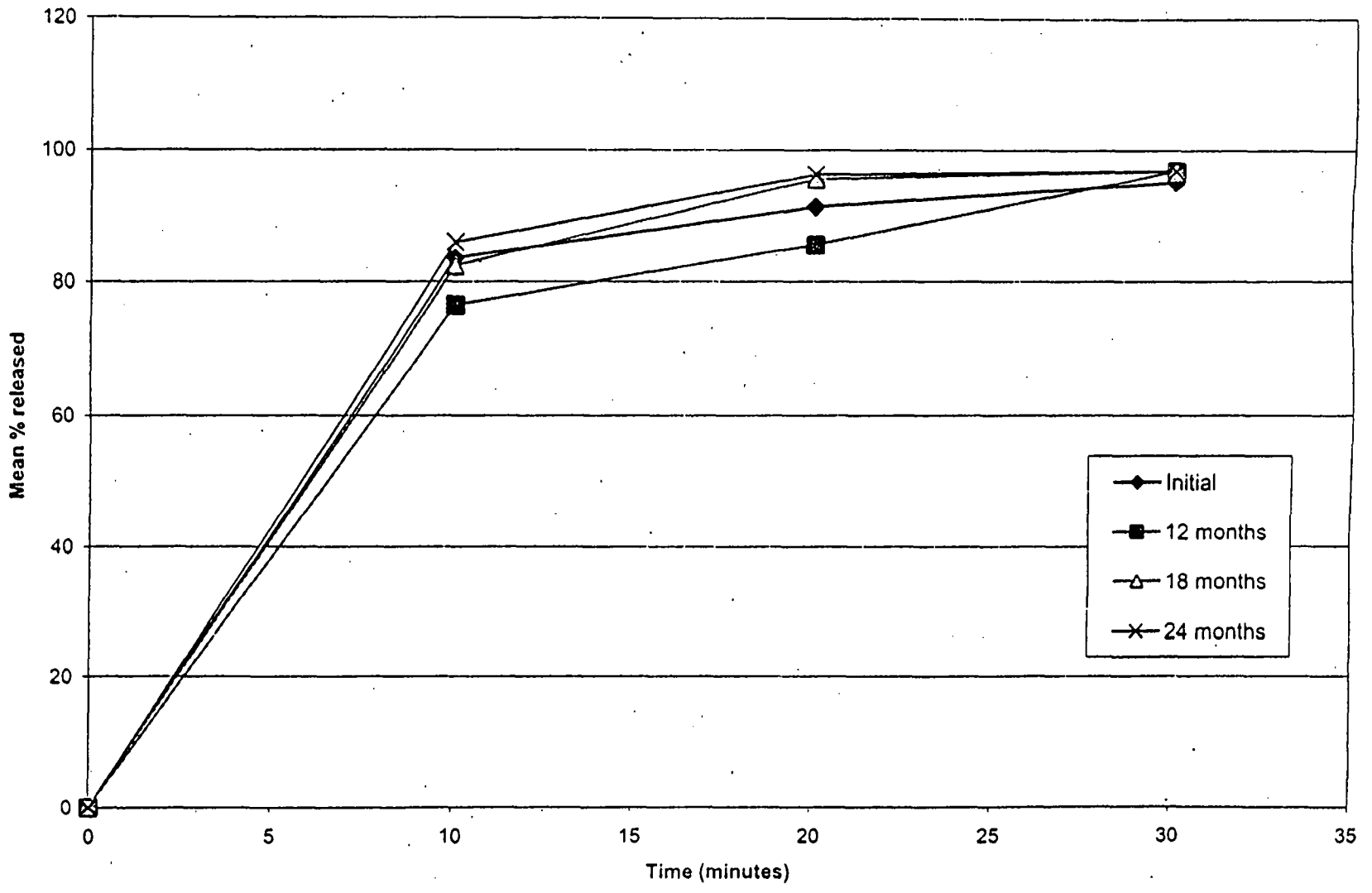
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							83.5	2.9
	20							91.4	2.0
	30							95.1	2.0

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							76.5	5.6
	20							85.6	4.7
	30							96.8	3.5

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							82.4	5.6
	20							95.5	1.6
	30							96.9	1.9

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							85.9	2.2
	20							96.2	1.1
	30							96.8	1.1

QT493 VML 251 2.5mg Tablets Batch number SB005 packed in — stored at 25°/60% RH



diss_acl.xls QT493 chart

QT498 VML 251 2.5mg Tablets Batch number SB006 packed in ——— blisters stored at 25°/60% RH

Study Number QT498

Product Batch Number SB006

Start Date December 2, 1997

Container ———blisters

Storage conditions 25°/60% RH

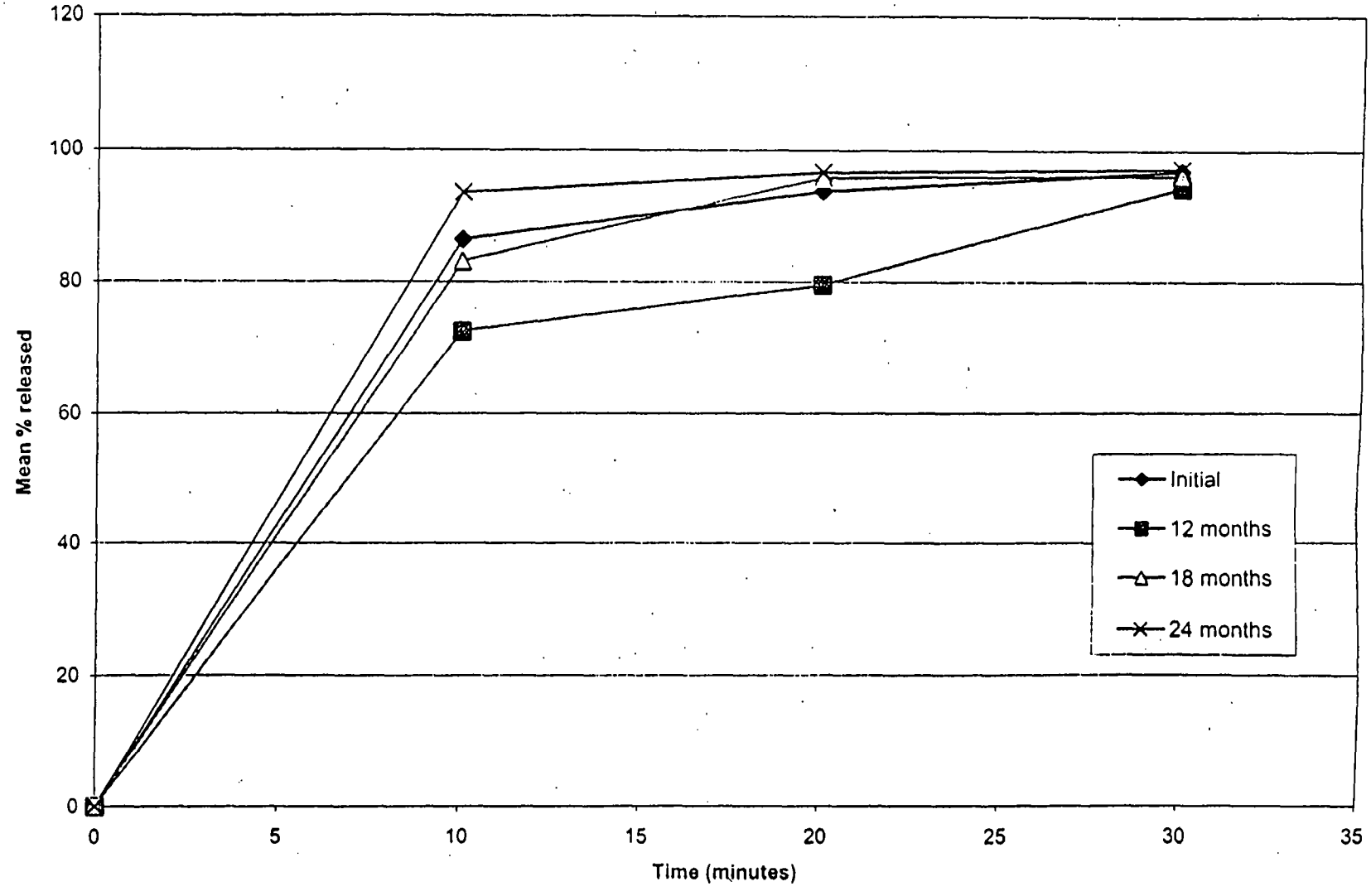
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							86.3	2.9
	20							93.7	1.3
	30							96.8	1.5

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							72.5	5.8
	20							79.5	4.4
	30							94.2	3.9

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							83.0	8.2
	20							95.8	2.0
	30							96.1	1.8

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							93.5	2.4
	20							96.6	1.5
	30							97.1	1.2

QT498 VML 251 2.5mg Tablets Batch number SB006 packed in —— blisters stored at 25°/60% RH



294 VML 251 2.5mg Tablets Batch number SB007 packed in blisters stored at 25°/60% RH (12m) and 30°/60% RH (18m)

Study Number 294

Product Batch Number SB007

Start Date May 25, 1998

Container blisters

Storage conditions 25°/60% RH

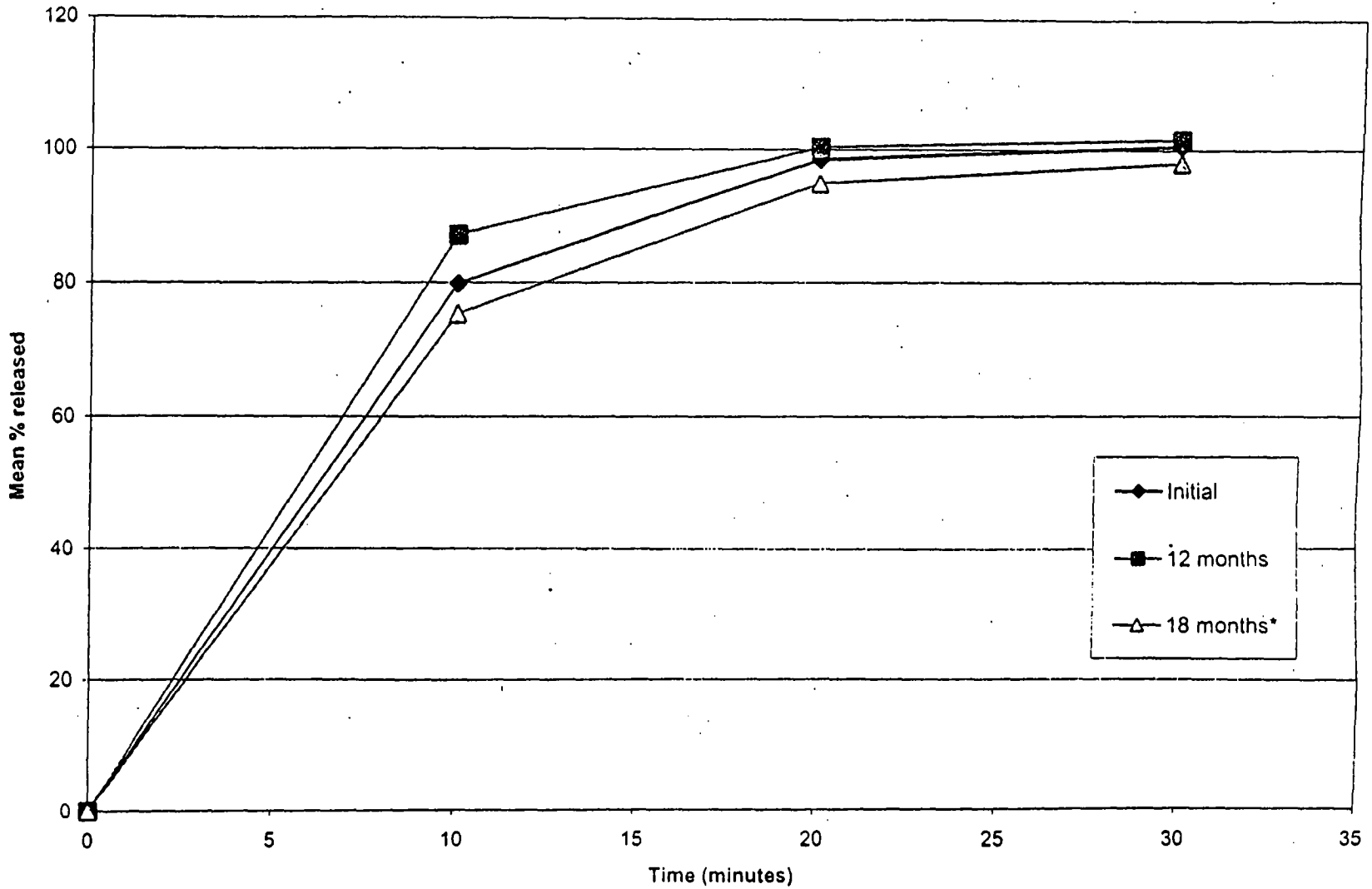
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							79.8	3.5
	20							98.5	2.6
	30							100.6	3.0

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							87.0	3.0
	20							100.3	1.6
	30							101.5	2.4

18 months*		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							75.3	5.5
	20							94.8	2.6
	30							98.0	1.4

* Data on tablets stored at 30°/60% RH

294 VML 251 2.5mg Tablets Batch number SB007 packed in blisters stored at 25°/60% RH (12m) and 30°/60% RH (18m)



QT528 VML 251 2.5mg Tablets Batch number SB001 packed in HDPE 100 count bottles stored at 25°/60% RH

Study Number QT528

Product Batch Number SB001

Start Date January 13, 1998

Container HDPE 100 count bottles

Storage conditions 25°/60% RH

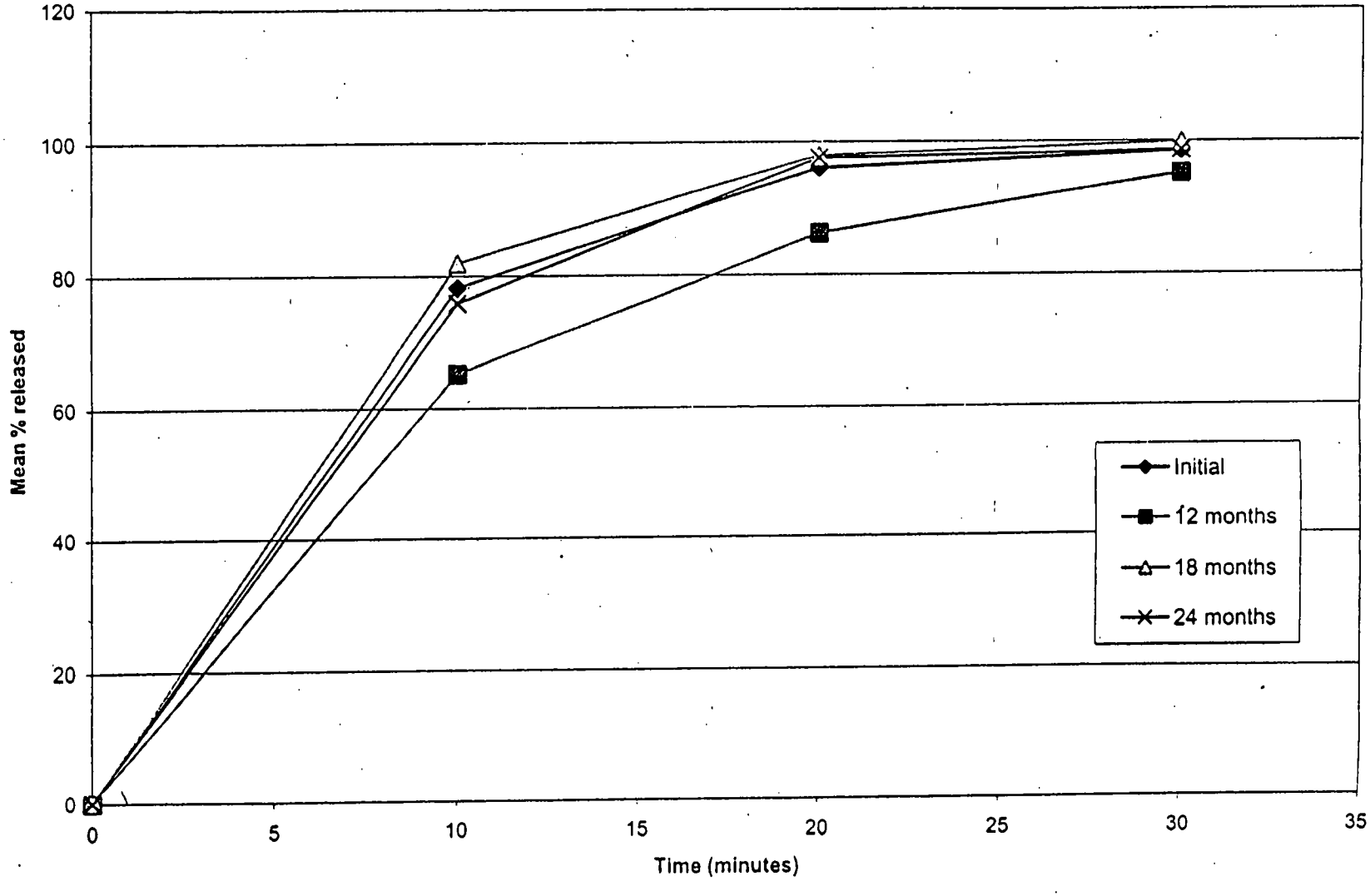
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							78.2	1.5
	20							96.0	1.9
	30							98.6	2.6

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							65.2	3.5
	20							86.1	8.7
	30							95.1	5.8

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							81.9	2.5
	20							97.9	3.7
	30							99.9	3.6

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	
Time point (mins)	0							0.0	0.0
	10							75.9	4.4
	20							97.6	2.7
	30							98.6	2.5

QT528 VML 251 2.5mg Tablets Batch number SB001 packed in HDPE 100 count bottles stored at 25°/60% RH



QT533 VML 251 2.5mg Tablets Batch number SB002 packed in HDPE 100 count bottles stored at 25°/60% RH

Study Number QT533

Product Batch Number SB002

Start Date January 13, 1998

Container HDPE 100 count bottles

Storage conditions 25°/60% RH

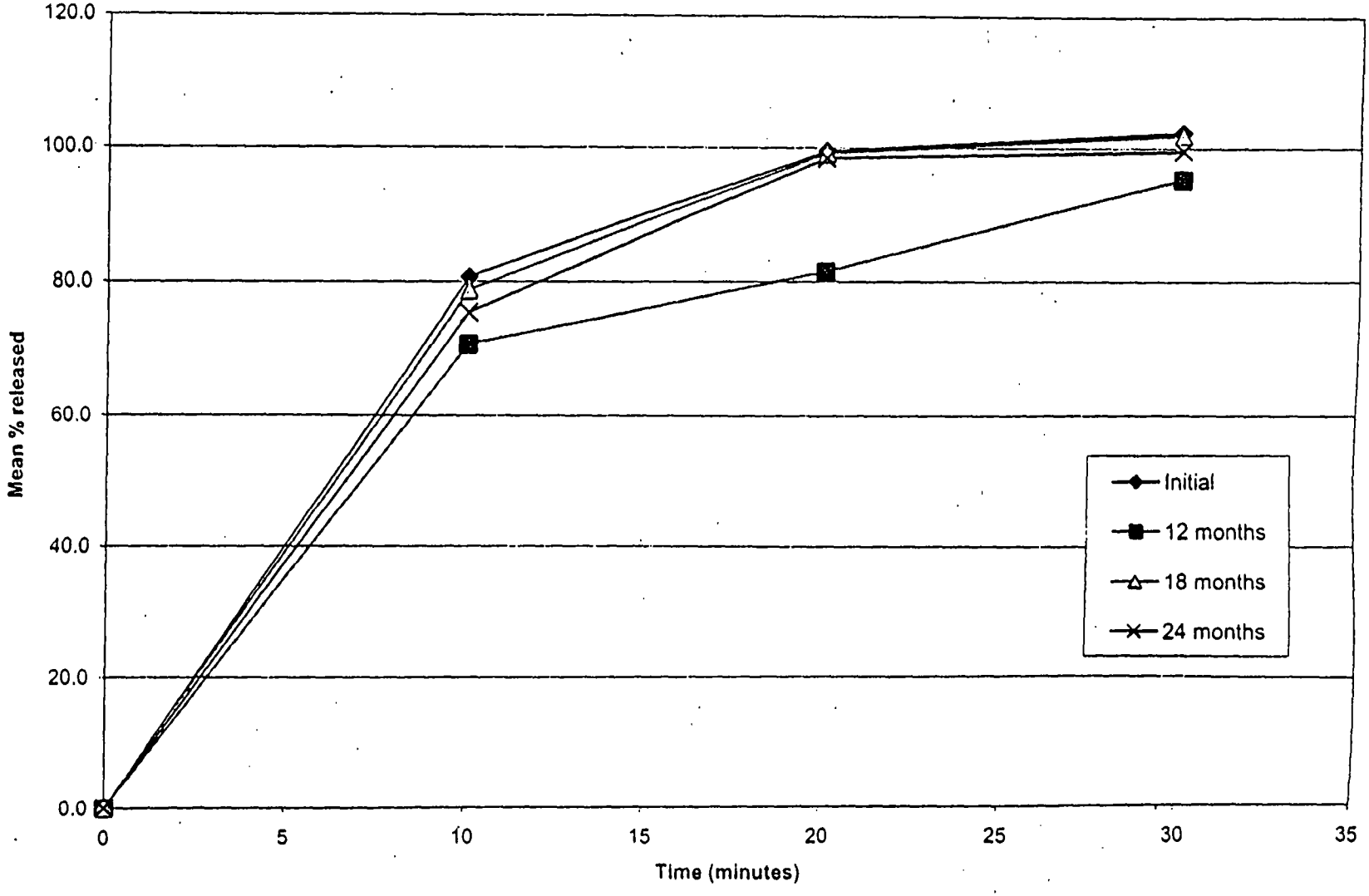
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							80.7	2.8
	20							99.4	1.4
	30							102.4	1.5

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							70.7	1.4
	20							81.4	6.2
	30							95.2	3.4

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							78.7	6.5
	20							99.1	3.3
	30							102.0	2.6

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	
Time point (mins)	0							0.0	0.0
	10							75.4	5.1
	20							98.4	2.6
	30							99.6	2.1

QT533 VML 251 2.5mg Tablets Batch number SB002 packed in HDPE 100 count bottles stored at 25°/60% RH



QT522 VML 251 2.5mg Tablets Batch number SB004 packed in HDPE 100 count bottles stored at 25°/60% RH

Study Number QT522

Product Batch Number SB004

Start Date January 13, 1998

Container HDPE 100 count bottles

Storage conditions 25°/60% RH

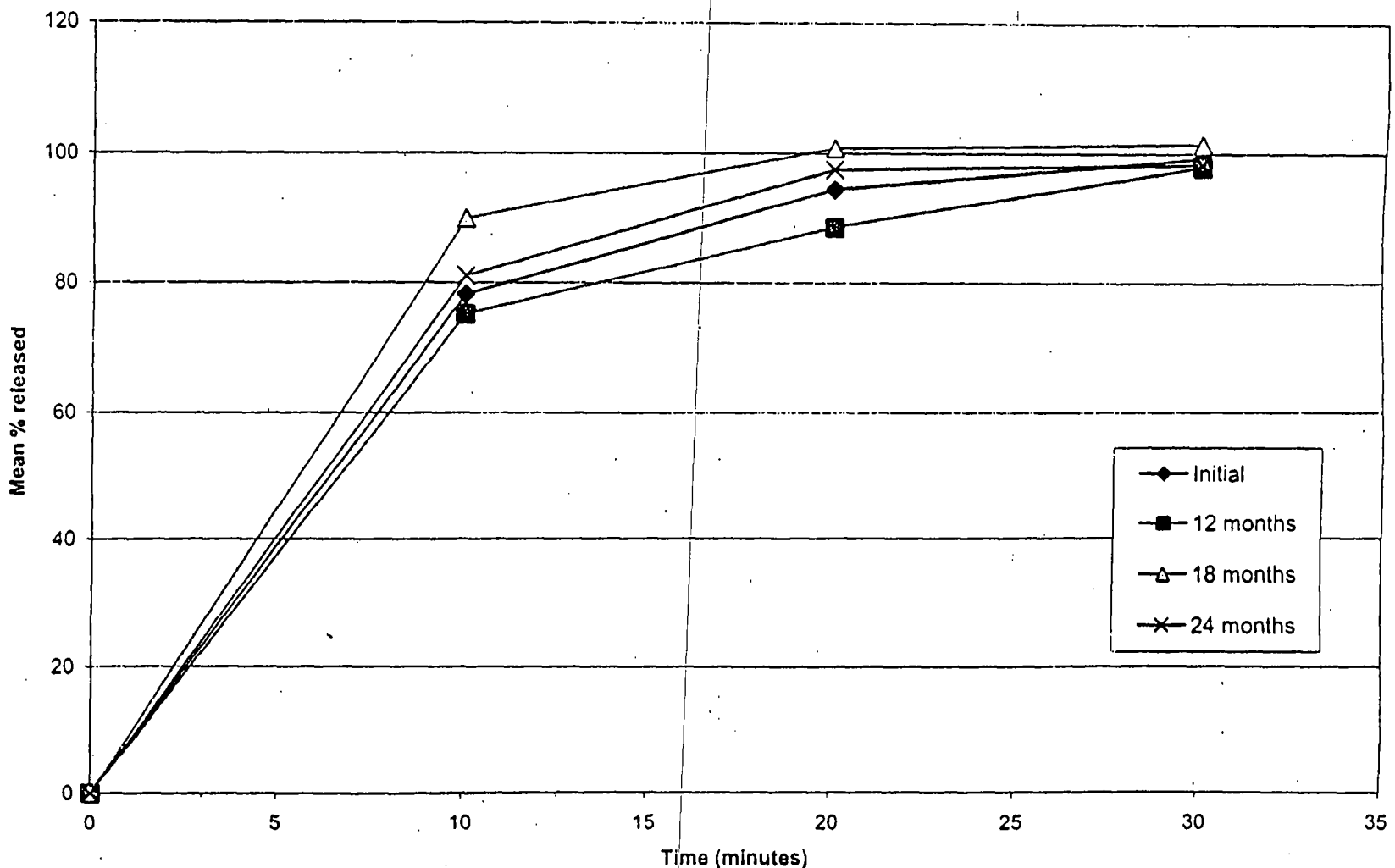
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							78.3	4.0
	20							94.4	2.5
	30							99.3	2.2

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							75.2	1.5
	20							88.5	6.8
	30							97.9	3.0

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							89.9	4.6
	20							100.8	2.0
	30							101.4	2.3

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							81.0	4.1
	20							97.4	3.3
	30							98.3	3.1

QT522 VML 251 2.5mg Tablets Batch number SB004 packed in HDPE 100 count bottles stored at 25°/60% RH



QT496 VML 251 2.5mg Tablets Batch number SB005 packed in HDPE 100 count bottles stored at 25°/60% RH

Study Number QT496

Product Batch Number SB005

Start Date December 2, 1997

Container HDPE 100 count bottles

Storage conditions 25°/60% RH

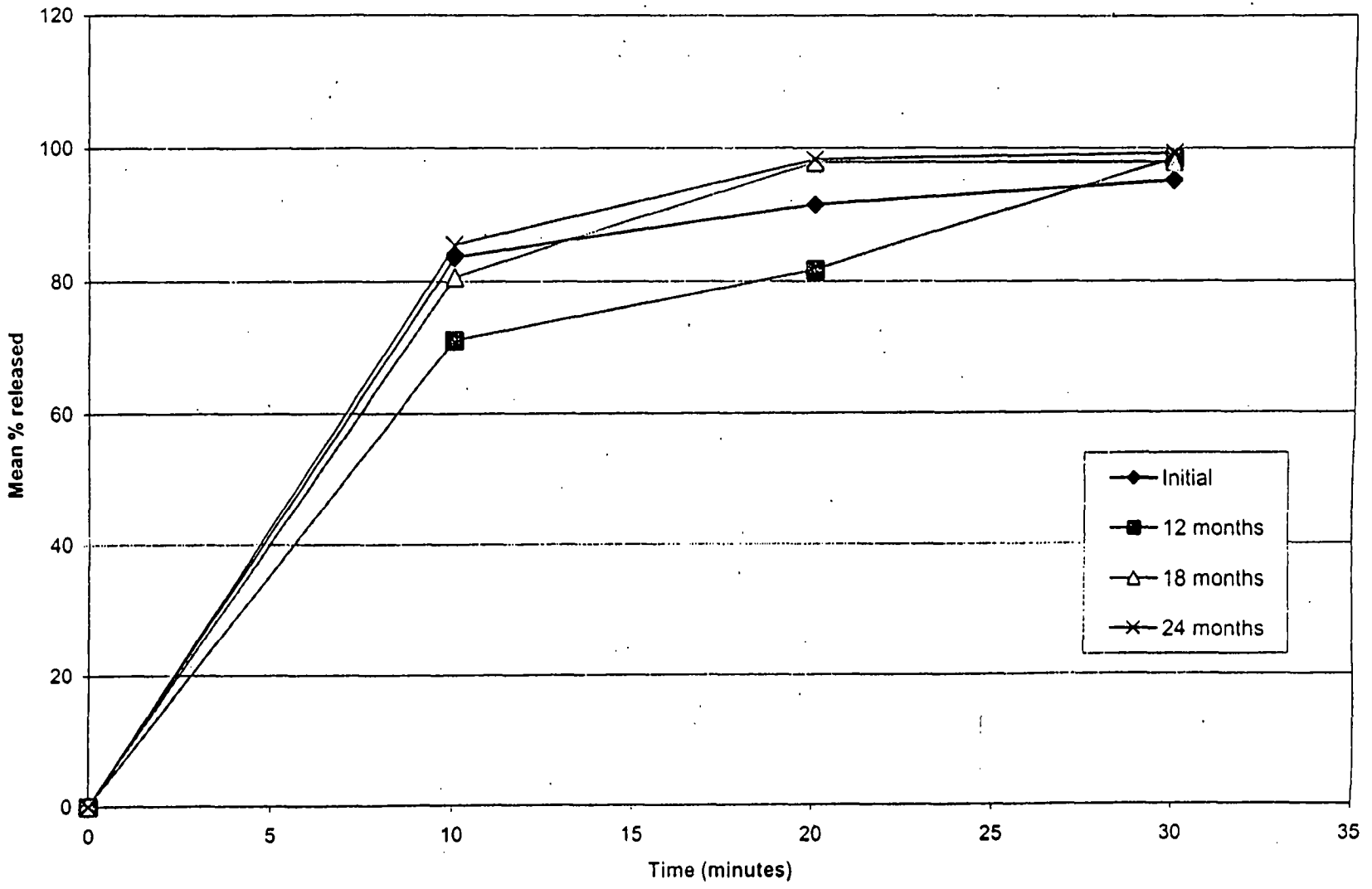
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							83.5	2.9
	20							91.4	2.0
	30							95.1	2.0

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							71.1	2.7
	20							81.7	8.2
	30							98.4	2.4

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							80.6	3.7
	20							97.7	1.9
	30							97.8	1.8

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	
Time point (mins)	0							0.0	0.0
	10							85.3	2.5
	20							98.2	1.8
	30							99.3	1.7

QT496 VML 251 2.5mg Tablets Batch number SB005 packed in HDPE 100 count bottles stored at 25°/60% RH



QT501 VML 251 2.5mg Tablets Batch number SB006 packed in HDPE 100 count bottles stored at 25°/60% RH

Study Number QT501

Product Batch Number SB006

Start Date December 2, 1997

Container HDPE 100 count bottles

Storage conditions 25°/60% RH

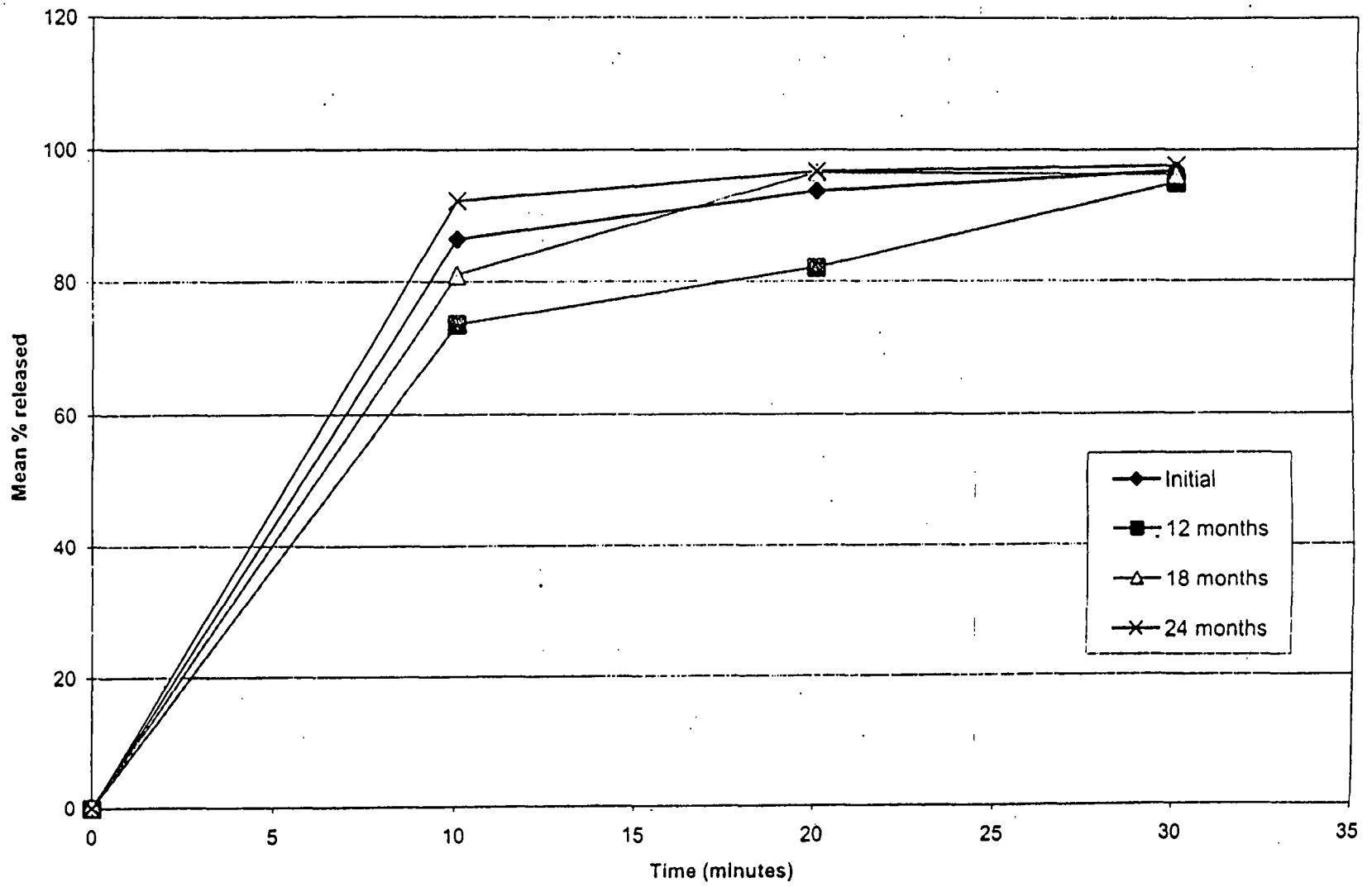
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							86.3	2.9
	20							93.7	1.3
	30							96.8	1.5

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							73.6	3.2
	20							82.0	1.9
	30							94.9	3.0

18 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							80.9	4.5
	20							96.5	0.6
	30							96.2	0.5

24 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							92.1	2.7
	20							96.7	0.7
	30							97.6	0.5

QT501 VML 251 2.5mg Tablets Batch number SB006 packed in HDPE 100 count bottles stored at 25°/60% RH



293 VML 251 2.5mg Tablets Batch number SB007 packed in HDPE 100 count bottles stored at 25°/60% RH (12m) and 30°/60% RH (18m)

Study Number 293

Product Batch Number SB007

Start Date May 25, 1998

Container HDPE 100 count bottles

Storage conditions 25°/60% RH

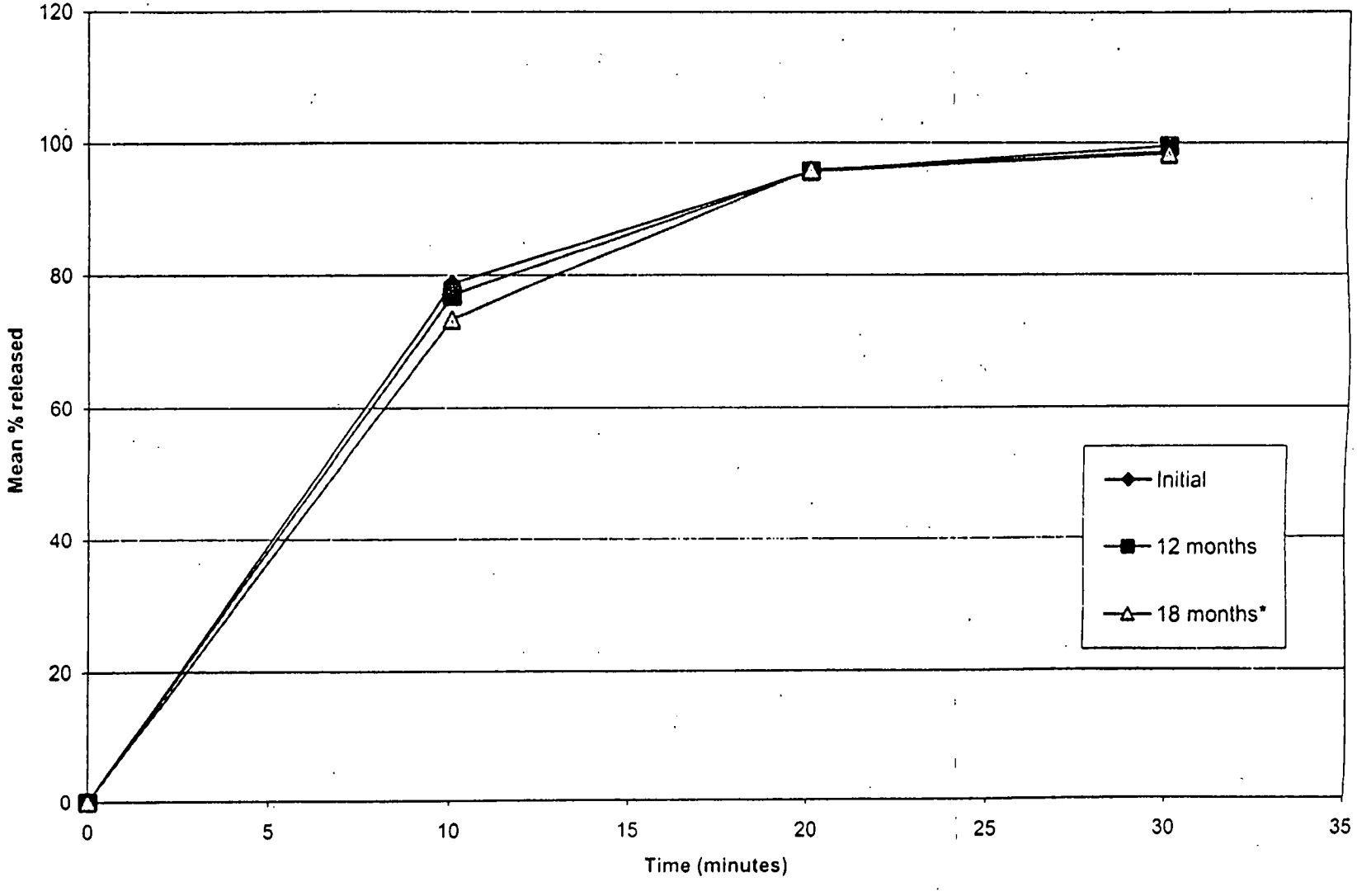
Initial		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							78.7	4.7
	20							95.8	1.5
	30							98.6	1.4

12 months		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							77.0	1.9
	20							95.8	1.6
	30							99.5	2.3

18 months*		Vessel						Statistics	
		1	2	3	4	5	6	Mean	SD
Time point (mins)	0							0.0	0.0
	10							73.5	3.5
	20							96.0	2.2
	30							98.3	1.5

* Data on tablets stored at 30°/60% RH

293 VML 251 2.5mg Tablets Batch number SB007 packed in HDPE 100 count bottles stored at 25°/60% RH (12m) and 30°/60% RH (18m)



OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Frovatriptan Succinate Monohydrate (MIGUARD™)
2.5 mg tablets
NDA 21-006

Vanguard Medica Limited,
Chancellor Court, Surrey Research Park
Guildford, Surrey GU2 5FS, UK

Authorized U.S. Agent:

[redacted]

Submission Dates:
January 29, 1999; February 25, 1999;
September 29 1999; October 21, 1999

Reviewers: Maria Sunzel, Ph.D., Iftekhar Mahmood, Ph.D.

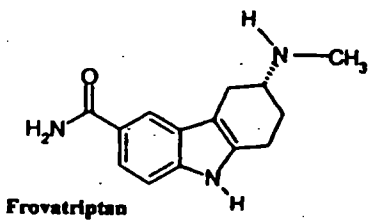
Indication: Migraine Treatment

Submission Type: Original – New Molecular Entity

SYNOPSIS

Frovatriptan (MIGUARD™) is a selective 5-hydroxy-tryptamine (5-$HT_{1B/1D}$) receptor subtype agonist, and has been shown to constrict human isolated cerebral arteries, with little effect in isolated human coronary arteries. Frovatriptan is intended for the treatment of acute migraine attacks as a single dose of 2.5 mg. The Sponsor recommends maximum daily dose intake of 7.5 mg (3 doses of 2.5 mg over 24 h). The clinical efficacy has been determined in three pivotal trials, about 40% of the patients responded to treatment 2 h after dose intake, and about 60% 4 h after dose intake. A change in headache intensity from moderate-severe to mild or no headache was classified as a response. Most patients suffering from migraine are female, and in the clinical studies 88% of the patients were females.

The immediate release tablets are white and film-coated with a round shape. The tablets contain the monosuccinate monohydrate salt of frovatriptan, corresponding to 2.5 mg free base. Frovatriptan is a single enantiomer with R-configuration (+), and the chemical structure is shown below:



Frovatriptan

Mw: 243.31 (free base), 379.41 (salt)
pKa: 9.93
Aqueous solubility (salt): >100 mg/mL at pH ≥ 3
Non-hygroscopic, white to off-white powder

Frovatriptan pharmacokinetics and biopharmaceutics may be summarized as follows:

- C_{max} is reached 2-4 h after tablet intake
- Absolute bioavailability: 20-30%
- Food had no effect on the pharmacokinetics of frovatriptan, though t_{max} was prolonged by an hour under fed condition as compared to fasting
- The commercial 2.5 mg frovatriptan tablet was bioequivalent to 2.5 mg round tablets and [redacted] used in clinical trials

- Plasma protein binding 15%; Red blood cell binding 60%; time-dependent whole blood:plasma ratio 2:1
- Vss: 3 L/kg
- Approximately 32% of total radioactivity was excreted in urine and 62% excreted in feces after an oral dose of ^{14}C-labelled frovatriptan. After an i.v. dose (unlabelled drug): 30-40% of frovatriptan was excreted via urine (unchanged drug)
- Metabolism partly via CYP 1A2, metabolic pathways: dèmethylation, N-acetylation and hydroxylation. Frovatriptan does not induce or inhibit cytochrome P450 isoenzymes in therapeutic concentrations
- Total clearance (i.v.) about 220 mL/min (males) and 130 mL/min (females); renal clearance (p.o.) 50-60 mL/min (males and females) p.o.; low extraction ratio drug
- Terminal half-life: 26 h
- Dose proportional increase in AUC and C_{max} with increasing single doses 2.5-40 mg
- Acute migraine headache may influence the pharmacokinetics of frovatriptan in female, but not male patients
- Elderly have approximately 2-fold higher AUC and C_{max} values compared to young volunteers
- Females have 2-fold higher AUC and C_{max} values compared to males
- Compared to young healthy male or female subjects without contraceptives, the $AUC_{(0-t)}$ of frovatriptan was almost 2-fold higher in patients with hepatic impairment (inconclusive study).
- There is no difference in the pharmacokinetic parameters of frovatriptan between healthy volunteers and patients with reduced renal function (inconclusive study).
- Frovatriptan was co-administered with propranolol, moclobemide, ergotamine and oral contraceptives. Overall, these drugs did not exhibit any significant pharmacokinetic interaction with frovatriptan. Oral contraceptives may inhibit frovatriptan metabolism in females (30% increase in AUC).

TABLE OF CONTENTS

STUDY SUMMARIES:

Study # 1: Study VML 251/96/12: A Phase I, open, randomly balanced, three-way cross-over, comparative pharmacokinetics study in male and female volunteers, at single doses of 2.5 mg (oral), 40 mg (oral) and 0.8 mg (IV)

Study # 2: Study 1165/34: A Phase I, open, randomised, balanced, 3-way crossover study to assess the safety, tolerability and pharmacokinetics of a single oral (40 mg —— and solution formulations) and intravenous (1.2 mg) doses of SB 209509 in healthy male volunteers

Study #3: Study VAD5-01: A single-dose, two-way crossover study to determine the effects of food on the bioavailability of SB 209509 ——

Study #4: Study VML 251/97/05: VML 251 - A phase I, open label, randomly-balanced, three way crossover study in healthy female subjects to investigate the bioequivalence of three different formulations of VML 251 administered as single oral dose of 2.5 mg on each occasion

Study #5: Study 1165/62: SB 209509 A phase I, open, balanced, 4-way crossover study in healthy male volunteers to investigate the bioequivalence of three different tablet strengths and one —— strength at a dose level of 40 mg

Study #6: Study 1165/43: A phase I, open balanced 3 way crossover study in 24 healthy male volunteers to investigate the bioequivalence of three different —— strengths at an oral dose level of 20 mg

Study # 7: Report DR93118: ^{3}H-SB 209509-A: Binding to rat, dog, and human serum proteins

Study # 8: Report DR93030: Time and concentration dependence of the red blood cell binding of ^{3}H-SB 209509-A in cat, dog, and human blood

Study # 9: Report 1165/192-D1140: ^{14}C-VML 251: Assessment and validation of a method for the separation of blood cells and determination of blood binding distribution

Study # 10: Study 1165/24: A Phase I, single-blind, placebo-controlled, single ascending, oral and intravenous dose study to assess the safety, tolerability, pharmacokinetics and the absolute bioavailability of SB 209509 in healthy male volunteers

Study # 11: Report 3185FR1/VT470-608-678: Determination of CYPs involved in VML 251 metabolism, evaluation of CYP inhibitory and induction properties of VML 251: *In vitro* experiments

Study # 12: Report 1165/83-1006: ^{14}C-VML 251: Metabolism in subcellular fractions isolated from human liver

Study # 13: Report VML/BRI/0198: The interactions of VML 251 and its desmethyl-derivative with amine oxidases

Study # 14: Study 1165/48-1011: ^{14}C-SB 209509: A study of the absorption, metabolism and excretion following oral administration to healthy human volunteers

Study # 15: Study 1165/135 (VML 251/98/01): ^{14}C-VML 251: An investigation of circulating and excreted metabolites following a single oral dose to male and female human subjects

Study # 16: Study 1165/42: A Phase I, single-blind, placebo-controlled, single ascending, oral dose study to assess the safety, tolerability, pharmacokinetics of SB 209509 in healthy male volunteers

Study # 17: Study 251/96/04: A phase I, open study to investigate the pharmacokinetics and intra-individual variability of two single oral doses of 40 mg VML 251 in healthy male and female volunteers

Study # 18: Study 251/96/01: A double-blind, placebo-controlled study in healthy subjects to investigate the safety, tolerability and pharmacokinetics of multiple doses of VML 251 (SB 209509)

Study # 19: Study 251/96/03: A double-blind, randomized, placebo-controlled study to determine and compare the tolerability and pharmacokinetic profile of two different dosage regimens of VML 251 in healthy male and female volunteers

Study # 20: Study 251/95/01: A single (patient) blind, dose-titration study to assess the safety, tolerability, pharmacokinetics, and clinical efficacy of single oral doses of VML 251 (SB 209509), in the range 2.5 mg-40 mg, in the acute treatment of migraine

Study # 21: Study 251/97/04: VML 251 - A phase II, open-label, crossover, comparative pharmacokinetic study in male and female patients administered with a single oral dose of 2.5 mg VML 251 both during a moderate to severe migraine attack and outside a migraine attack

Study # 22: Study 251/97/01: VML251 - A phase I, open, single oral dose comparative pharmacokinetic study in elderly male and female subjects at a dose of 2.5 mg

Study #23: Study 251/97/06: An open label, single oral dose, comparative pharmacokinetic study of 2.5 mg VML 251 in male and female patients with mild to moderate hepatic impairment

Study #24: Study 251/97/02: An open label, single oral dose, comparative pharmacokinetic, two center study of 2.5 mg VML 251 in male and female patients with varying degree of renal impairment and healthy male and female volunteers

Study # 25: Study 251/98/06: An open label pharmacokinetic study of the potential interaction between VML 251 and propranolol in healthy male and female subjects.

Study # 26: Study 251/98/07: An open label, randomly-balanced, crossover comparative pharmacokinetic study to investigate a possible interaction between moclobemide and VML 251

Study # 27: Study 251/98/02: VML 251- An open label, randomly-balanced, three way crossover comparative safety and pharmacokinetic study in healthy female subjects administered with a single oral dose of VML 251 5 mg alone, when co-administered with 2 mg ergotamine tartrate or 2 mg ergotamine tartrate given alone

Study # 28: Retrospective analysis of the pharmacokinetic interaction between frovatriptan and oral contraceptives in females

Study # 29: Dissolution

Study # 30: Formulation

Study # 31: Bioanalytical methods

A total of 21 phase I studies were submitted and reviewed in this NDA. In addition, six pre-clinical (metabolism, inhibition, induction, blood- and plasma-binding), and one pharmaceutical (dissolution) study were reviewed.

QUESTIONS IN THE SUBMISSION

1. Is the time-dependency for the equilibrium between whole blood and plasma (about 2 h *in vivo*) important for the pharmacokinetics of frovatriptan?
2. How well is the metabolism of frovatriptan characterized *in vivo*?
3. Should special dosing recommendations be given for any group in 'special populations'?

1. ABSORPTION

Absorption and bioavailability:

The time to reach maximal frovatriptan blood concentrations, t_{max}, is approximately 2-4 h, after oral administration of oral solution, ——— and tablets of frovatriptan (2.5, 40 mg). [Study #1 and #2]

The absolute bioavailability of frovatriptan (2.5 mg tablet orally, 0.8 mg i.v. infusion) was about 20% in young males (n=6) and 30% in young females (n=6). [Study #1] The absolute bioavailability was similar for ——— (12%) and oral solution (11%) after 40 mg oral doses, and 1.2 mg i.v. infusion. [Study #2]

Food effect:

The effect of food on the pharmacokinetics of frovatriptan was assessed in 12 healthy volunteers (3 males and 9 females). Each subject received 2 x 20 mg ——— orally either under fasting state (10 hours) or following FDA recommended high fat meal. Based on 90% confidence interval on log transformed AUC(0-inf) and C_{max}, food had no effect on the pharmacokinetics of frovatriptan.

Confidence interval:

AUC(0-inf) = 89 – 124%
C_{max} = 84 – 112%

However, the t_{max} was approximately an hour longer in the fed state as compared to fasting. [Study #3]

Bioequivalence studies:

A: In a three way crossover bioequivalence study, 21 female volunteers (under fasting state) received a single oral dose of 3 different formulations of frovatriptan:

Round tablet: 2.5 mg
——— 2.5 mg
Commercial tablet: 2.5 mg.

A seven day wash out period separated each dosing administration. The round tablets and ——— were used in previous clinical trials. The study indicated that the 90% confidence interval for all three formulations was within the required range of ——————— for C_{max} and AUC. [Study #4]

This bioequivalence study was conducted only in female subjects. According to the Sponsor, the study was conducted in females because they have comparatively higher blood levels of frovatriptan than males. Furthermore, according to the Sponsor, females also represent the majority of target population.

B: In a four way crossover bioequivalence study, 32 healthy male volunteers received (under fasting state) a single dose of frovatriptan orally as follows:

Tablet: 16 x 2.5 mg
Tablet: 4 x 10 mg
Tablet: 1 x 40 mg
[redacted] 4 x 10 mg

A seven day wash out period separated each dosing administration. The objective of this study was to compare 2.5, 10 and 40 mg tablets with 10 mg [redacted] (reference) used in previous clinical trials at a dose of 40 mg. The study indicated that all three tablet formulations were bioequivalent to [redacted] as the 90% confidence interval was within the required range of [redacted] for C_{max} and AUC (Study #5). Though there were 32 subjects in this study, the bioequivalence criteria was applied only on 24 subjects (1-24). According to the Sponsor, 23 subjects were sufficient to detect a difference of greater than 20% in AUC with 80% power at a 5% significant level. The Sponsor was requested to reanalyze this BE study by including all 32 subjects. In a teleconference on September 29, 1999, the Sponsor informed the reviewers (Sunzel and Mahmood) that they never measured frovatriptan blood concentrations in the remaining 8 subjects and blood samples from these 8 subjects have been already discarded. Despite the fact that this is not a pivotal bioequivalence study, the Sponsor should have measured the concentration of frovatriptan in all 32 subjects and included the data from all subjects in their confidence interval analysis. [redacted]

C: In a 3 way crossover bioequivalence study, the following dosage strengths of frovatriptan were administered to 24 healthy male volunteers (under fasting state).

[redacted] : 8 x 2.5 mg
[redacted] 2 x 10 mg
[redacted] : 1 x 20 mg

A seven day wash out period separated each dosing administration. The study indicated that the 90% confidence interval for all three strengths of [redacted] was within the required range of [redacted] for C_{max} and AUC. [Study #6)] Thus the three strengths of frovatriptan [redacted] were considered to be bioequivalent.

2. DISTRIBUTION

Whole blood and protein binding:

In vitro studies have shown that frovatriptan has a low protein binding of about 15%, which is linear for frovatriptan concentrations ranging from 2.4 to 1220 ng/mL, in human serum. The maximal concentration (1220 ng/mL) is well above therapeutic concentrations attained after a 2.5 mg dose. Frovatriptan binds to reversibly to red blood cells to about 60%, with a whole blood-to-plasma ratio of about 1.3 and 2.0 *in vitro* and *in vivo*, respectively. This distribution to red blood cells is time dependent, and equilibrium from plasma to blood is attained approx. 0.75 h (*in vitro*) and 2 h (*in vivo*) after drug administration. Another *in vitro* study showed that about 30% frovatriptan binds to erythrocytes, 20% to platelets, 15% to plasma, and the remainder (35%) was recovered in leukocyte and cell-free fractions. [Studies #7, #8, #9]

Volume of distribution:

After a 30-min i.v. infusion (0.8 mg), the mean volume of distribution ($V_{\lambda 2}$) was 6.7±2.3 L/kg and 4.6±1.4 L/kg in young male and female subjects, respectively. The corresponding values of

the mean volume of distribution at steady state (Vss) were 4.2±1.5 L/kg and 3.0±0.9 L/kg [Study #1]. The Vss in male subjects was about 30% lower in two other studies (Study #10 and #2).

3. METABOLISM

3.1. In vitro studies

Metabolism:

In human hepatocyte and microsome (human and recombinant cells) preparations, 10-20% of frovatriptan was metabolized via CYP1A2 to desmethyl frovatriptan (0.3-3.9%) and desmethyl N-acetyl frovatriptan (0.5-2.5%), the major metabolite formed (0.6-9.9%) was unidentified. In the human hepatocytes frovatriptan metabolism was abolished in the presence of a CYP 1A2 inhibitor (furafylline), but no effect was observed during co-incubation with inhibitors for CYP 2C9, 2D6, or CYP 3A4. [Studies #11 and #12]

Inhibition:

Frovatriptan did not inhibit the metabolic activity of substrates for CYP 1A2, 2C8/2C9, 2C19, 2D6, 2E1 or CYP 3A4. [Study #11]

Induction:

Frovatriptan has no induction properties on CYP 1A2, CYP 4A or CYP 3A4 activities. [Study #11]

The experiments were performed at concentrations that are well above therapeutic levels after a 2.5 mg dose of frovatriptan. However, the results in the *in vivo* studies are in concurrence with the observed *in vitro* results.

Monoamine oxidase (MAO):

Both frovatriptan and desmethyl frovatriptan were shown to reversibly inhibit MAO-A activity at high concentrations (IC_{50}'s in human liver mitochondria of 1.1 mg/mL and 0.5 mg/mL, respectively). The compounds did not significantly inhibit MAO-B activity at very high concentrations. Frovatriptan inhibited semicarbazide-sensitive amine oxidase (SSAO) activity at concentrations above 243.3 ng/mL, (65% inhibition at 6.08 mg/mL). Desmethyl frovatriptan was not tested in the system. Frovatriptan and desmethyl frovatriptan were not substrates for MAO (no H_2O_2 formation during incubation). The IC_{50} value for MAO-A inhibition is well above concentrations of frovatriptan observed after a 2.5 mg dose (10 ng/mL). Therefore, frovatriptan and desmethyl frovatriptan are not likely to be affected by concomitant administration of MAO-inhibitors. [Study #13]

3.2. In vivo studies

Metabolism:

In the two studies where ^{14}C-labelled frovatriptan was administered orally to healthy subjects (40 mg, n=4; 2.5 mg oral solution, n=4), the desmethyl and N-acetyl desmethyl metabolites were recovered in urine and feces. The metabolite identification is rather sketchy, since a thorough metabolite identification analysis was only undertaken for one subject per sample. [Study #14 and #15]. For mass-balance data, see Section 4, ELIMINATION.

In urine, the recovery of the total dose of desmethyl and N-acetyl desmethyl metabolites were 2.4% and 3.6%, respectively (mean values, n=4). A major (11%), unidentified peak, less polar than frovatriptan, was subsequently identified as N-acetyl desmethyl frovatriptan, and two hydroxy metabolites. *Note:* approx. 10% of the total dose was excreted as unchanged frovatriptan in urine. [Study #15]

In feces, the major metabolite formed was the indole carboxylic acid of frovatriptan (9.4% of total dose), and the recovery of desmethyl and N-acetyl desmethyl metabolites were <1% for both metabolites (mean values, n=4). *Note:* 32% of the total dose was excreted as unchanged frovatriptan in feces. [Study #15]

The proposed metabolic pathways of frovatriptan are depicted in Fig. 1.

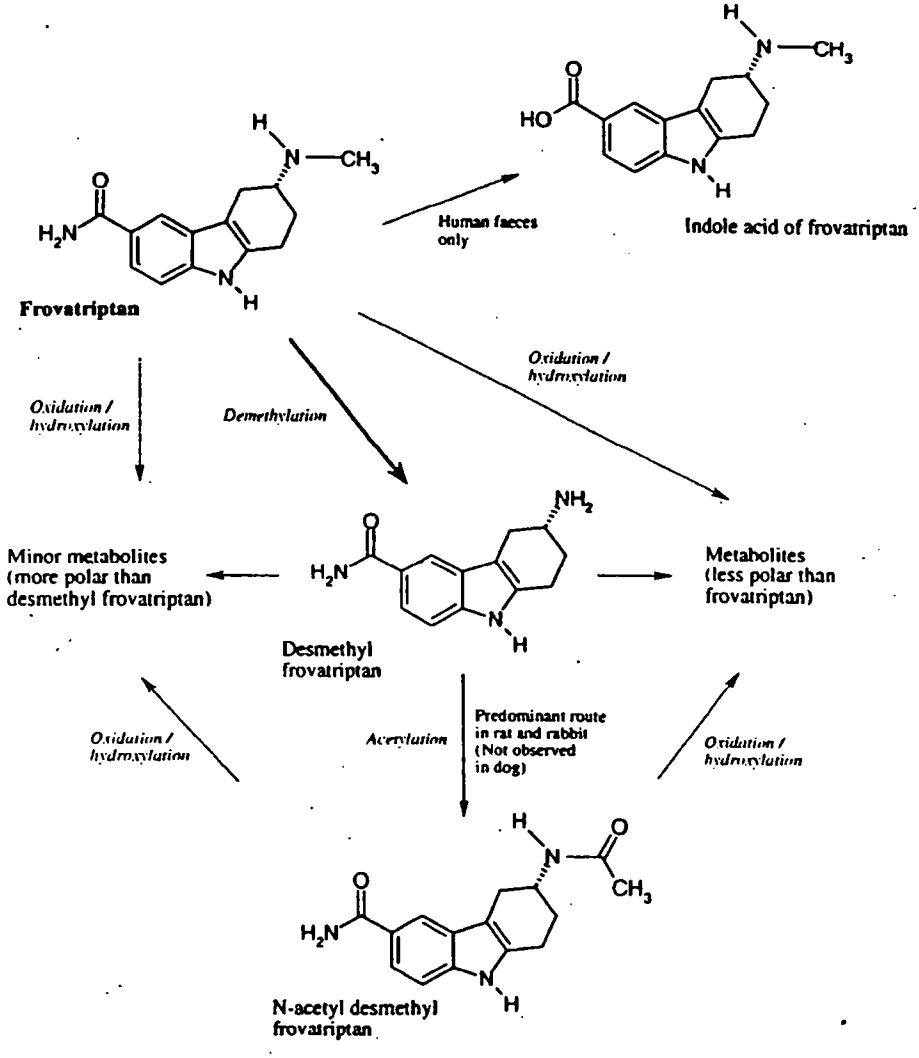


Figure 1. Proposed metabolic fate of frovatriptan

Chiral inversion:

Frovatriptan is administered as the (+) isomer, and does not undergo isomerisation to the (–) isomer *in vivo*. [Study #1]

4. ELIMINATION

Excretion:

After oral administration of ^{14}C-labelled frovatriptan to healthy subjects (n=4), the major amount of total radioactivity, 61.8±15.5%, was excreted in feces (32% unchanged drug), and the remainder in urine, 31.5±7.4% (10% unchanged drug). Since no intravenous dose was administered, it is not possible to determine if the large fraction excreted via feces is due to incomplete absorption or in part, due to excretion via bile. [Study #15] After 0.8 mg unlabelled frovatriptan given as an i.v. infusion, 30-40% of the dose is excreted via urine as unchanged drug. [Study #1]

Clearance:

After an i.v. administration of 0.8 mg frovatriptan, the total clearance was calculated to about 220 mL/min and 130 mL/min for males (n=6) and females (n=5), respectively. The renal clearance (CL_R) after the i.v. infusion was determined to 82 mL/min and 60 mL/min for males and females, respectively. The CL_R after an oral dose of 2.5 mg was 50 mL/min and 60 mL/min for males and females, respectively. Based on the total and renal clearance after i.v. administration, frovatriptan has a low hepatic extraction ratio (E_H=0.11). [Study #1 and #2]

Half-life (frovatriptan and metabolites):

The terminal half-life (t½) of frovatriptan is about 26 h, with an initial t½ (post-absorption) of about 2.5 h.

Desmethyl frovatriptan has a terminal t½ of about 71 h and 93 h in males and females, respectively. The maximal blood concentrations (C_{max}) of the desmethyl metabolite are approx. 70-80% lower than the parent compound, but the AUCs of the desmethyl metabolite and frovatriptan are similar, due to the slow elimination of the metabolite. The t½ of N-acetyl desmethyl frovatriptan has not been determined due to low metabolite blood concentrations after oral doses. [Study #1]

5. PHARMACOKINETICS IN HEALTHY VOLUNTEERS

Dose linearity:

Oral single doses of frovatriptan, administered as ——→, or tablets, have been given in the range of 1 mg to 100 mg in the phase I studies. Since no study explored the full dose range, the data described in this section is pooled (male volunteers) from several studies. Frovatriptan has been extensively studied in doses of 40 mg or lower, and as shown in Figure 2, there is a linear increase in $AUC_{0-\infty}$ with increasing doses of frovatriptan. The corresponding C_{max} values also increased in a dose-proportional manner. [Studies #1, #2, #5, #6, #10, #16, #17, and #25]

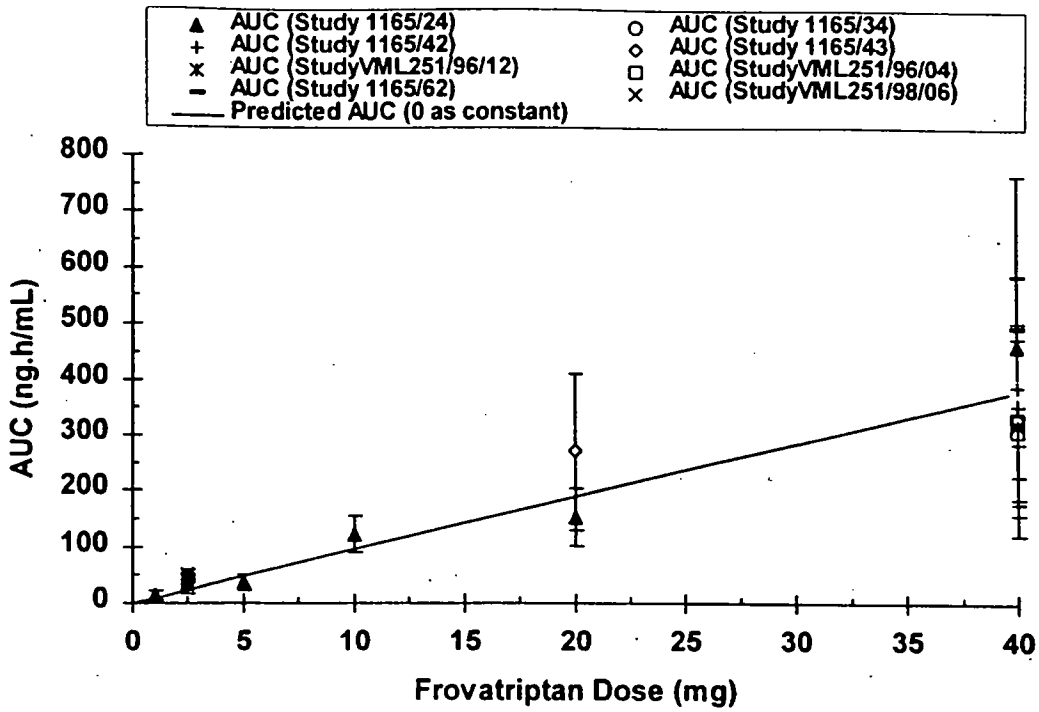


Figure 2. $AUC_{0-\infty}$ (mean±SD) *vs.* dose after oral administration of frovatriptan as —— or tablets in young healthy male volunteers

Inter- and intra-individual variability:

The inter- and intra-individual variability after a single dose of 40 mg frovatriptan have been studied in healthy male and female volunteers (12F/12M). The inter-individual variability for AUC and C_{max} of frovatriptan was high, 40-50% in male and female volunteers. However, the intra-individual variability in the volunteers for the parameters was lower, 16-19%. There were no apparent gender differences in the inter- and intra- individual variability. [Study #17]. The high inter-individual variability has also been observed in most other studies.

Repeated dosing:

Multiple doses of frovatriptan have been evaluated in healthy male and female volunteers only at higher doses of 10 mg (7F/8M), 20 mg (7F/8M), or 40 mg. Two different dosing regimens were studied, 1) b.i.d. doses of 40 mg frovatriptan during 5 days, and 2) three consecutive single doses (10, 20 or 40 mg/dose) at 0 h, 2 h, and 12 h during the investigational day. [Study #18 and #19]
1) After 5 days of 40 mg frovatriptan b.i.d. the accumulation ratio (R_{AC}) was higher, 1.79, in females (n=4) compared to the R_{AC} of 1.50 in males (n=3).

2) The three consecutive single doses were less well tolerated in females than males after the 20 and especially the 40 mg doses. Two of the four females discontinued dosing due to adverse events (AEs) after the 2nd 40 mg dose, and one of eight females discontinued dosing due to AEs after the 2nd 20 mg dose. All males completed the studies, and all females completed the 3x10 mg dose regimen. Due to the relatively slow absorption and long t½, the 2nd dose 2 h after the first, approximately doubles the blood concentrations of frovatriptan.

The 2.5 mg dose has not been studied after three consecutive single administrations in healthy volunteers. Since a total dose of 30 mg administered within 12 h was tolerated in both female

and male subjects, a total daily dose of 7.5 mg should be acceptable. The dosage regimen (3 x 2.5 mg daily) has been studied in one clinical long-term efficacy study in migraine patients.

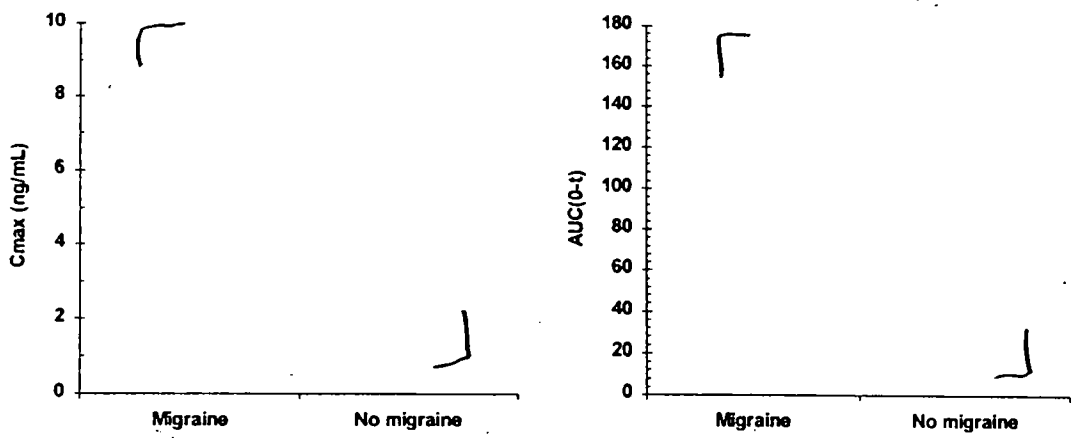
6. PHARMACOKINETICS IN PATIENTS

Patients during or outside a migraine attack:

Two studies, without placebo control, have been performed in patients suffering of migraine headaches. In one larger study (62 patients, 52F/10M) single doses of 2.5-20 mg frovatriptan were administered during a migraine attack, and drug concentrations in blood were followed for 6 h after dosing. There was a less than dose proportional increase in AUC_{0-6h} and C_{max} for the doses. However, due to the uneven number of patients assigned to different dose levels and the short blood-sampling period, which may have lead to underestimation's of AUC and C_{max}, these results are less reliable than the phase I studies. [Study #20]

The second study was performed in 12 patients (6F/6M), where all patients were given a 2.5 mg frovatriptan dose at the onset of a migraine attack, and a second 2.5 mg dose outside an attack. The pharmacokinetics of frovatriptan was unaltered during and outside a migraine attack in male patients. In the female patients, there was a delay in the mean t_{max} of about 1 h but the variability was large. There was no change in C_{max} during an attack compared to outside a headache. The AUC in the females increased about 30% on average during a migraine headache, but the increase was only seen in half of the female group, as shown in Figure 3. [Study #21]

Figure 3. C_{max} (left panel) and AUC_{0-t} (right panel) values for females (solid lines; filled circles) and males (dashed lines; open circles) during and after a migraine attack (values without correction for bodyweight).



The pharmacokinetics of frovatriptan during a migraine attack is similar to outside a migraine attack. However, the females that showed increased AUCs during the headache period, had very large changes.

7. PHARMACOKINETICS IN SPECIAL POPULATIONS

7.1. Age

Frovatriptan has not been studied in subjects younger than the age 18.

In elderly subjects (6F/6M, mean age 69) the pharmacokinetics of frovatriptan has only been studied after a single 2.5 mg dose, and a historical comparison has been made to young volunteers (6F, mean age 29; 6M, mean age 31; Study #1). [Study #22] After dose and bodyweight normalization, elderly females had 30-35% higher AUC and C_{max} compared to elderly males. The elderly males had almost 2-fold higher AUC and C_{max} compared to the young

males, and the elderly females had about a 40% increase in AUC and C_{max} compared to the young females, see Table 1. The difference in AUC between elderly and young females may be explained by a 35% reduction in the renal CL in the group of elderly females.

Table 1. Arithmetic mean (SD) of the pharmacokinetics of frovatriptan in whole blood after single doses of 2.5 mg frovatriptan in elderly and young healthy volunteers (values without correction for bodyweight).

Age (mean; min-max)	Gender	n	AUC 0-t (ng.h/mL)	AUC0-∞ (ng.h/mL)	Cmax (ng/mL)	tmax (h)	t½ (h)
Elderly (69; 65-77)	Males	6	66 (16)	75 (16)	5.8 (1.4)	3.3 (0.6)	20.3 (2.6)
Elderly (69; 66-74)	Females	6	130 (86)	141 (91)	9.7 (4.4)	3.2 (1.4)	22.5 (5.5)
Young* (31; 27-36)	Males*	6	34 (8.1)	43 (7.4)	4.4 (1.2)	2.3 (0.3)	27.4 (14.1)
Young* (29; 21-37)	Females*	6	88 (29)	98 (31)	7.1 (0.9)	3.1 (0.8)	25.7 (5.6)

*Results from Study #1

The gender difference observed in young volunteers persists in the elderly population however, the difference in C_{max} and AUC between males and females is reduced to 30% (elderly) from 100% (young). The difference between elderly male and female volunteers may be explained by the 35% reduction in renal clearance in the elderly females compared to the elderly males, 33 mL/min and 51mL/min, respectively. The inter-individual variability was about twice as high for the elderly female volunteers compared to the elderly male volunteers. The elderly females have about 40% higher C_{max} and AUCs compared to the young healthy female volunteers. This difference may be greater, since five of the six young female volunteers participating in Study VML 251/96/12 were taking oral contraceptives concomitantly with frovatriptan.

7.2. Gender

After oral doses the AUC and C_{max} is approximately doubled in young female subjects compared to young male subjects, but t_{max} and t½ are similar in both groups. The difference is only partly explained by the 10% higher absolute bioavailability and the 33% reduction in total clearance after an i.v. dose in women compared to men. The volume of distribution (Vss) was also higher in females, 3 L/kg *vs.* 4.2 L/kg in men. [Study #1]

Since this is the only study where both oral and intravenous doses have been given to female and male subjects, it is difficult to assess what major factor that contributes to the observed difference. However, the dissimilarity in clearance is possibly the most important pharmacokinetic determinant of the observed difference.

7.3. Hepatic impairment

The pharmacokinetics of frovatriptan was assessed in 8 subjects with mild (n = 4, Child-Pugh Score = 5-6) and moderate (n =4, Child-Pugh Score = 7-9) hepatic impairment [Study #23]. There were 2 males and 2 females in each group. The age of the patients ranged from 44 to 57 years. There was no control group in this study. The subjects received 2.5 mg frovatriptan as a single oral tablet. Compared to young healthy male (n =6, age = 31 years) or female subjects without contraceptives (n =9, age = 33 years), the AUC(0-t) of frovatriptan was almost 2 fold higher in patients with hepatic impairment. The C_{max} of frovatriptan was slightly higher in male patients with hepatic impairment as compared to healthy male subjects, but the C_{max} was 2 fold higher in female patients with hepatic impairment as compared to healthy female subjects. The half-life of frovatriptan was almost 10 hours shorter in males with hepatic impairment than the healthy male subjects. This may be due to the fact that the data from hepatic impairment patients

were compared with historical data from healthy subjects. The half-life of frovatriptan was comparable in females with and without hepatic impairment. However, the AUC, C_{max} and half-life of frovatriptan were comparable between healthy elderly subjects (both male and females) and patients with hepatic impairment. The coefficient of variation (CV%) on the AUC in patients with hepatic impairment was more than 50% both in males and females. The Sponsor claims that hepatic impairment has no effect on the pharmacokinetics of frovatriptan. However, in this study, the number of patients with hepatic impairment is inadequate to make such a conclusion. This study is inconclusive.

The Sponsor has not conducted the hepatic impairment study using adequate sample size. In the submitted study, the comparison between the healthy elderly subjects and the subjects suffering from hepatic impairment is also inappropriate. The mean age of healthy elderly subjects is 69 years whereas mean age in hepatically impaired group is about 54 years. Since age increases the AUC of frovatriptan by 100% in males and 40% in females, it is difficult to conclude whether difference in the AUC of frovatriptan between the healthy subjects and in patients with hepatic impairment is due to liver impairment or age. Furthermore, there is an obvious difference in the pharmacokinetics of frovatriptan between young healthy subjects and patients with hepatic impairment. The sample size is also too small to draw any conclusion. Thus the present study is inconclusive.

7.4. Renal impairment

The pharmacokinetics of frovatriptan was assessed in patients with mild (Cr CL = > 60-80 mL/min, 2 females), moderate (Cr CL = >30-60 mL/min, 2 females and 4 males) and severe (Cr CL =10-30 mL/min, 2 females and 1 male) renal impairment (18-60 years). There were age-matched 3 females and 4 males in control group (Cr CL = > 80 mL/min). The subjects received a 2.5 mg frovatriptan as a single oral dose. The results indicated that there is no difference in the pharmacokinetic parameters of frovatriptan between healthy volunteers and patients with reduced renal function. [Study #24] Like the hepatic impairment study, this study is also inconclusive.

The sample size is not adequate to detect difference among different groups of patients with renal impairment. Furthermore, there is also effect of gender on the pharmacokinetics of frovatriptan (at least 2 fold higher blood levels in women than men). Therefore, a small sample size with both males and females data lumped together may not depict the real effect of renal impairment on the pharmacokinetics of frovatriptan.

8. DRUG-DRUG INTERACTIONS

8.1. Frovatriptan-Propranolol

Propranolol is frequently used as a prophylactic agent for migraine. Therefore, a drug-interaction study between propranolol and frovatriptan was conducted. This was randomized, open-label, two-period, crossover study. The study was initiated in 14 young healthy subjects (6 males and 8 females) of ages ranging between 18 to 29 years. Twelve subjects (6 males and 6 females) completed the study. Two subjects withdrew due to personal reasons. The subjects received the following treatment:

Treatment A: Propranolol 80 mg, bid, orally on days 1-7 and a single oral dose of 2.5 mg frovatriptan tablet on day 8 with the morning dose of propranolol and a final dose of 80 mg propranolol 12 hours later on day 8.

Treatment B: A single oral dose of 2.5 mg frovatriptan tablet on the morning of day 1.

There was a 10-day washout period between each period. Blood samples were collected till 96 hours. Drug concentrations could not be detected beyond 48 hours. The extrapolated AUC was approximately 36% for men and 14% in women. Therefore, in this summary the comparison has been made based on AUC(0-48) hours.

Concomitant administration of frovatriptan with propranolol resulted in a significant increase in the AUC and C_{max} of frovatriptan. The AUC and C_{max} of frovatriptan in females was about 2 fold and 1.5 fold higher, respectively as compared to males. Propranolol increased the AUC of frovatriptan in males by 60% and in females by 29%. The C_{max} of frovatriptan was increased by 23% in males and by 16% in females in the presence of propranolol. The t_{max} as well as half-life of frovatriptan, though, slightly longer in the females were not affected by concomitant administration of propranolol. The amount of frovatriptan dose excreted unchanged in urine in males was 11% and 5.5% with and without propranolol, respectively. In females, the excretion of frovatriptan in urine was comparatively higher than males, representing 17% and12% with and without propranolol, respectively. However, propranolol did not effect the renal clearance of frovatriptan and also there was no gender difference in renal clearance of frovatriptan. Overall, this study suggests that dosage adjustment of frovatriptan may not be warranted when given with propranolol. The effect of frovatriptan on the pharmacokinetics of propranolol was not evaluated [Study #25].

8.2. Frovatriptan-Moclobemide

Moclobemide is a reversible selective inhibitor of MAO-A and is used in the management of depression. This was randomized, open-label, two-period, crossover study. The study was conducted in 12 healthy females of ages ranging between 19 to 32 years who were on contraceptives. Nine subjects completed the study. One subject withdrew due to adverse event of moclobemide (did not receive frovatriptan), the second subject was withdrawn from the study due to positive urine drug test and the third subject withdrew her consent before receiving moclobemide. The subjects received the following treatment:

Treatment A: Moclobemide 150 mg, bid, orally on days 1-7 and a single oral dose of 2.5 mg frovatriptan tablet on day 8 with the morning dose of moclobemide and a final dose of 150 mg moclobemide 12 hours later on day 8.

Treatment B: A single oral dose of 2.5 mg VML 251 tablet on the morning of day 1.

There was a 10-day washout period between each period. Blood samples were collected up to 96 hours. The extrapolated AUC of frovatriptan was approximately 13% without moclobemide and 48% in the presence of moclobemide. In the presence of moclobemide, the AUC(0-96) of frovatriptan was slightly lower (8%) but the AUC(0-inf) was 20% higher as compared to the AUCs when frovatriptan was given alone. The C_{max} and half-life of frovatriptan were comparable in the presence or absence of moclobemide, though t_{max} was 0.5 hour longer when frovatriptan was given with moclobemide. The amount of frovatriptan excreted unchanged in urine was about 11% with or without moclobemide.

Overall, this study suggests that dosage adjustment of frovatriptan may not be needed when given with moclobemide. The effect of frovatriptan on the pharmacokinetics of moclobemide was not evaluated (Study # 26).

8.3. Frovatriptan-Ergotamine

The effect of ergotamine, a potent central and peripheral vasoconstrictor, on the pharmacokinetics of frovatriptan was evaluated in 12 healthy female subjects (23 to 44 years). This was a randomly, balanced three-way crossover study. All subjects completed the study. The subjects received the following treatment:

Treatment A: Frovatriptan 5 mg

Treatment B: Frovatriptan 5 mg + ergotamine tartrate 2 mg sublingually

Treatment C: Ergotamine tartrate 2 mg alone

There was a 10 day washout period between each treatment. Blood samples were collected till 96 hours. In the presence of ergotamine, the AUC(0-inf) and C_{max} of frovatriptan was about 25% lower as compared to the AUC and C_{max} when frovatriptan was given alone. The half-life of frovatriptan was comparable in the presence or absence of ergotamine, though t_{max} was 0.5 hour longer when frovatriptan was given with ergotamine.

Overall, this study suggests that dosage adjustment of frovatriptan may not be needed when given with ergotamine. It should be noted that a 25% reduction in C_{max} of frovatriptan when given with ergotamine might produce a subtherapeutic blood level. However, in the absence of plasma concentration vs effect relationship such a notion (therapeutic or subtherapeutic) is difficult to establish. The effect of frovatriptan on the pharmacokinetics of ergotamine was not evaluated [Study #27].

8.4. Frovatriptan-Oral contraceptives

A systematic study to evaluate the effect of oral contraceptives on the pharmacokinetics of frovatriptan has not been conducted. However, a retrospective analysis was performed from pooled data (2.5, 5 and 40 mg doses of frovatriptan). Overall, in these studies there were 34 women who received frovatriptan with contraceptives and 55 women received frovatriptan without contraceptives. The result of this evaluation indicated that the mean values of frovatriptan for C_{max} and AUC were 25% and 30% higher in the group of women who were on contraceptives as compared to those who were without contraceptives. According to the Sponsor, analysis of data in the clinical trials showed no clinically relevant differences in safety or efficacy in female patients without and with estrogen therapy, the majority of which were on oral contraceptives. Therefore, based on the pooled data analysis, the Sponsor claims that there is no need to adjust frovatriptan dose in women who are taking oral contraceptives.

9. PHARMACOKINETICS/PHARMACODYNAMICS

No attempts were made to relate the blood concentrations of frovatriptan to any pharmacodymanic measure. In Study # 20 the whole blood concentration of frovatriptan was compared to the pain relief of the migraine attack at 2 h post-dose, but no relationship was established. The effective dose producing 50% of pain relief was calculated to 4.5 mg (95% CI: 0.2-8.0 mg). In the large patient trials, no added effect was seen at doses above 2.5 mg of frovatriptan.

In vitro studies have shown that one of the metabolites, desmethyl frovatriptan, may have pharmacological activity, since its affinity for the 5-HT receptor binding sites was about 0.5 units (pKi values) lower than that of frovatriptan. Although the total exposure (AUC) is similar to that of frovatriptan, the potential contribution to the pharmacological activity of the metabolite is unclear. The clinical dose-response curve of frovatriptan is quite flat at doses above 2.5 mg, indicating that the desmethyl moiety does not add to the pharmacological effect. The desmethyl

N-acetyl moiety did not bind to the 5-HT receptor. Since the desmethyl N-acetyl metabolite is present *in vivo* only at very low blood concentrations, it is unlikely that this metabolite contributes to the pharmacological activity after frovatriptan administration.

10. DISSOLUTION

The Sponsor's proposed Dissolution Method and Specifications for frovatriptan tablets are as follows (Study #28):

Dosage Form:	Tablet
Strengths:	2.5 mg
Apparatus:	USP Apparatus II (Paddle)
Medium:	900 mL phosphate buffer (pH = 5.5)
Speed:	50 rpm
Sampling Times:	10, 20, and 30 minutes

Sponsor's proposed Specifications: Q = ——— minutes

Despite the repeated request, the Sponsor has not provided the details on dissolution. Therefore, the specifications of dissolution will be set when such details will be available.

11. FORMULATION

MIGUARD™ tablets, intended for marketing are immediate release tablets, containing 2.5 mg of frovatriptan (base) as succinate and are available as round, white, film-coated tablets.

Several formulations of frovatriptan (——— and film-coated tablets) have been used in clinical studies. The ——— formulations were used in early phase I studies. The ——— were of 1, 2.5 and 10 mg strengths (as base). Late phase I and early phase II studies used 2.5, 10 and 20 mg ——— The remainder of the clinical studies used tablets with film-coating. Initially the coating ——— and then switched to water-based film-coat. The commercial tablets also have a water-based film-coat. The phase III dose ranging study tablets were 0.5, 1, 2.5 and 5 mg. The pivotal phase III studies were performed with the 2.5 mg tablet (as base). The bioequivalence studies compared the phase III tablet, the phase IIB 2.5 mg tablet and the commercial tablet.

12. ANALYTICAL METHODS

Frovatriptan concentrations in whole blood, plasma and urine have been analyzed by using ——— . The limit of quantitation (LOQ) for frovatriptan was — ng/mL, —ng/mL, and —ng/mL in whole blood, plasma and urine, respectively. An analytical method ——— for determination of (+) and (-) frovatriptan was also developed. Analysis methods ——— for determination of metabolite concentrations in whole blood (desmethyl frovatriptan and N-acetyl desmethyl frovatriptan) were also developed.

13. COMMENTS

1. Despite the fact that Study #5 (VML 1165/62) is not a pivotal bioequivalence study, the Sponsor should have measured the concentration of frovatriptan in all 32 subjects and included the data from all subjects in their confidence interval analysis.

2. The time-dependency for the equilibrium between whole blood and plasma (about 2 h *in vivo*) is most likely unimportant for the pharmacokinetics of frovatriptan. All bioanalyses where frovatriptan concentrations were determined were performed in both whole blood and plasma. Therefore whole blood concentrations are an adequate measure, and would reflect the 'true' pharmacokinetic profile of frovatriptan. However, more importantly, the question is if total clearance is higher before the equilibrium has been established between whole blood and plasma. Frovatriptan is only bound to 15% to plasma proteins, therefore both non-renal and renal clearance may be time-dependent, with an initial higher rate 1-2 h after dose-intake. Nevertheless, even if clearance is initially higher, the pharmacokinetics of frovatriptan has been sufficiently described.

3. The *in vivo* metabolism of frovatriptan is to some extent unclear. The metabolite identification performed in the studies with ^{14}C-labelled frovatriptan does not give a full picture of the metabolite pattern, since only one sample from one subject for each biological fluid was further used to compare biotransformation between different species. However, of primary interest, the metabolite identification in urine and feces does not raise the same concern, therefore the suggested metabolic pathways of frovatriptan seems acceptable, although somewhat sketchy.

4. Vital information of absorption of frovatriptan would have been collected if an i.v. dose had been included in the studies with ^{14}C-labelled frovatriptan. With the available information it is difficult to assess if the recovery of total radioactivity of 62% in feces is due to incomplete absorption, or potentially, frovatriptan excretion via bile.

5. The AUC and C_{max} in elderly are increased 2-fold compared to the young population. Since the clinical (phase II-III) studies include a very limited number of elderly (10 of 2 300 patients). Therefore, the importance of the increased exposure of frovatriptan in clinical practice for the elderly is unclear.

6. The Sponsor has not conducted the hepatic impairment study using adequate sample size. In the submitted study, the comparison between the healthy elderly subjects and the subjects suffering from hepatic impairment is also inappropriate. The mean age of healthy elderly subjects is 69 years whereas mean age in hepatically impaired group is about 54 years. Since age increases the AUC of frovatriptan by 100% in males and 40% in females, it is difficult to conclude whether difference in the AUC of frovatriptan between the healthy subjects and in patients with hepatic impairment is due to liver impairment or age. Furthermore, there is an obvious difference in the pharmacokinetics of frovatriptan between young healthy subjects and patients with hepatic impairment. The sample size is also too small to draw any conclusion. Thus the present study is inconclusive.

7. The sample size is not adequate to detect difference among different groups of patients with renal impairment. Furthermore, there is also effect of gender on the pharmacokinetics of frovatriptan (at least 2 fold higher blood levels in women than men). Therefore, a small

sample size with both males and females data lumped together may not depict the effect of renal impairment on the pharmacokinetics of frovatriptan.

14. LABELING COMMENTS

The Sponsor is requested to incorporate the following changes in the labeling text:

1. Please exchange the 2nd sentence, 1st paragraph, Pharmacokinetics section (p #3):

[redacted]

2. Food delays the t_{max} of frovatriptan almost by an hour. For a migraine patient, a delay of an hour in pain relief may be of significant importance. Therefore, labeling should clearly state that food delays t_{max} by an hour not [redacted] as stated by the Sponsor in their labeling (page #4, first 2 lines).

3. Pharmacokinetics, 4th paragraph, 2nd sentence (p #4):
   Please exclude the [redacted] in the sentence describing the urinary excretion. Since the percentages only reflect the content from one early urinary collection interval (4-8 h) after oral administration, the numbers may be confounding.
   The new sentence will read:
   Radiolabeled compounds excreted in urine were unchanged frovatriptan, hydroxylated frovatriptan, N-acetyl desmethyl frovatriptan, hydroxylated N-acetyl desmethyl frovatriptan, and desmethyl frovatriptan, together with several other minor metabolites.

4. Pharmacokinetics, 4th paragraph, 3rd sentence (p #4):

[redacted]

5. The study related to the effect of hepatic impairment on the pharmacokinetics of frovatriptan is inconclusive. Therefore, the statement that [redacted] may be misleading (Sponsor's labeling: page #12). In the absence of a conclusive study related to the effect of hepatic impairment on the pharmacokinetics of frovatriptan the labeling should read as follows (Sponsor's labeling; pages #4 and #12):

[redacted]

6. [redacted]

7. Drug interactions (page #5): Propranolol and frovatriptan interaction:
   The last sentence on page #6 should be replaced by the following:
   Propranolol increased the AUC of frovatriptan in males by 60% and in females by 29%. The C_{max} of frovatriptan was increased by 23% in males and by 16% in females in the presence of propranolol. The t_{max} as well as half-life of frovatriptan, though, slightly longer in the females were not affected by concomitant administration of propranolol.

8. Dosage and administration (page #20):

[ ]

APPEARS THIS WAY
ON ORIGINAL

15. RECOMMENDATION

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. The specifications of dissolution will be set when detailed information is obtained from the Sponsor.

The Sponsor is requested to incorporate all labeling changes.

Please forward the comments and the labeling changes to the Sponsor.

Maria Sunzel, Ph.D., /S/ 11/10/99

Iftekhar Mahmood, Ph.D., /S/ 11/10/99

RD initialed by Vijay Tammara, Ph.D., /S/ 11/11/99

FT initialed by Vijay Tammara, Ph.D., /S/ 11/10/99

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: November 5, 1999; Attendees: Drs. Larry Lesko, Mehul Mehta, Chandra Sahajwalla, Armando Oliva, Martha Heimann, Sidney Stolzenberg, John Lazor, Mei-Ling Chen, Paul Hepp, Wendy Chou, Vijay Tammara, Iftekhar Mahmood, and Maria Sunzel

c.c.: NDA 21-006, HFD-120, HFD-860 (Sunzel, Mahmood, Tammara, Mehta), HFD-340 (Viswanathan), CDR (Biopharm) and FOI files (HFD-19)

APPEARS THIS WAY
ON ORIGINAL