

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020103, S015

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-103/ SE1-015

Submission Date: 8/27/1998, 4/20/1999

Trade Name: Zofran[®] Tablets

Stamp Date: 8/28/1998, 4/21/1999

Active Ingredient: Ondansetron hydrochloride

Review Date: 6/4/1999

Sponsor: Glaxo wellcome Inc.

Draft Date: 8/18/1999

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Final Review Date: 8/20/1999

Type of Submission: Supplemental NDA for Higher Strength Zofran Tablets

Synopsis

Ondansetron tablets 8 mg BID and TID are currently approved for prevention of nausea and vomiting in moderately emetogenic chemotherapy regimens. However, due to the increased use of highly emetogenic chemotherapeutics in oncology practice, a need exists for a safe and effective antiemetic therapy. It is theorized that having high levels of the serotonin antagonist available to interact with 5-HT₃ receptors at the time of maximal release of serotonin (believed to take place 2-6 hrs following cisplatin treatment) would provide the greatest antiemetic efficacy. This suggested to the Firm that sustaining ondansetron plasma levels for 24 hrs was not necessary to maximize efficacy.

Supplemental NDA 20-103 to 24 mg ondansetron hydrochloride (Zofran[®]) tablets was submitted to the agency on August 27, 1997 for the prevention of nausea and vomiting induced by highly emetogenic chemotherapy. The Firm is seeking evaluation of the safety and efficacy of a single oral dose of ondansetron 24 mg for controlling emesis associated with highly emetogenic chemotherapy. On Apr 20, 1999, in response to Agency questions, the Firm submitted additional data demonstrating the bioequivalence between the clinical and to be marketed 24 mg Zofran formulations.

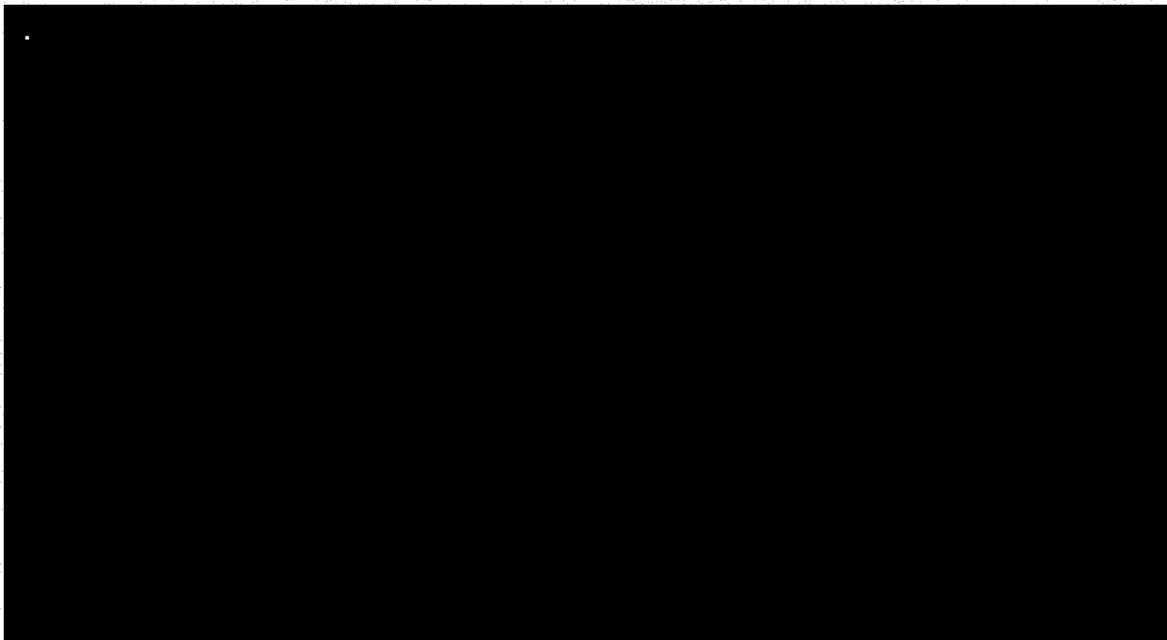
Background

Ondansetron is a potent, highly selective 5-HT₃ receptor antagonist. Oral ondansetron is well absorbed and undergoes limited first-pass metabolism. It is extensively metabolized in humans, with the primary metabolites resulting from hydroxylation on the indole ring followed by glucuronide or sulfate conjugation, with only 5% of a radiolabeled dose recovered from urine as parent compound. It is excreted through the urine and bile, with 44-53% of the dose being recovered in the urine within 24 hours of dosing. Administration of a single 8 mg ondansetron tablet to healthy, young male volunteers results in a t_{max} of 1.7 hrs, a terminal elimination half-life of 3 hrs and a bioavailability of 56%. At oral doses greater than 8 mg, C_{max} and AUC increase more than proportionally to dose, which might be due to saturation of first-pass metabolism. Bioavailability is slightly enhanced (17%) by the presence of food but unaffected by antacids. Ondansetron is not highly protein-bound (70-76%). Some unconjugated metabolites such as 8-hydroxyondansetron retain pharmacological activity. However, they are found in plasma at levels unlikely to contribute to the overall biological activity.

Objective

Evaluation of the safety and efficacy of single-dose 24 mg Zofran[®] tablets for the prevention of nausea and vomiting associated with the administration of highly-emetogenic cancer chemotherapy, including cisplatin.

Chemistry



Clinical Studies

Two US, randomized, double-blind, comparative, parallel, multicenter trials were conducted to evaluate the efficacy and safety of a single 24 mg oral dose of ondansetron for the prevention of chemotherapy-induced emesis and nausea (study S3AA3012 and S3AA3004/S3AA3007). One additional non-US, randomized, double-blind, parallel, multicenter trial was conducted to evaluate combination therapy of ondansetron plus dexamthasone, administered orally and intravenously (study S3AA3008) (see Table 2).

Two of the clinical efficacy studies (S3AA3012 and S3AB3008) used a clinical trial formulation ondansetron tablet 8 mg instead of the Zofran 8 mg tablet used in protocol S3AA1002. However, both tablet formulations have been previously shown to be bioequivalent (NDA 20-103/S-005).

Bioavailability and Human Pharmacokinetics Studies

To demonstrate interchangeability of the 8 mg and 24 mg Zofran tablets, a bioequivalence study was performed comparing a single ondansetron 24 mg tablet and three Zofran 8 mg tablets (study S3AA1002).

Reviewer's Comments

Supporting data has been submitted to show bioequivalence between the clinical trial and the to be marketed formulations for each of the 8 mg and 24 mg tablet formulations. The Firm conducted a study to demonstrate bioequivalence between the clinical and to be marketed formulations for 8 mg Zofran tablets (see appendix). As for the 24 mg ondansetron tablets, the clinical and to be marketed formulations were deemed interchangeable based on the similarity in formulation composition (see Chemistry Section).

S3AA1002

Objectives

To demonstrate bioequivalence between three 8 mg Zofran tablets and one 24 mg ondansetron tablet.

Study Design

Open, randomized, two-way crossover study

<u>Subjects</u>	16 male and female subjects (It was determined that 16 subjects should give this study a power of greater than 90% to declare bioequivalence at a significance level of 5%)
<u>Inclusion Criteria</u>	Healthy male or non-pregnant, non-lactating females 18-45 yrs of age Within 20% of ideal body weight
<u>Exclusion Criteria</u>	Known hypersensitivity to drugs with structures similar to ondansetron. History of any hematological, endocrine, cardiovascular, hepatic, renal, GI or pulmonary disorder. Tobacco use within past 2 months of study. Chronic use of any OTC or prescription drug.
<u>Dosing</u>	Either one 24 mg ondansetron tablet or three 8 mg Zofran tablets were administered with 200 ml water in randomized fashion.
<u>Washout</u>	3-7 days
<u>Sampling Times</u>	Serum samples collected prior to dosing, at 20, 40, 60, 90 min and at 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hrs post dose.
<u>Safety</u>	Subjects monitored for vital signs, ECG, lab test results and reported adverse events.
<u>PK</u>	C_{max} , t_{max} , $AUC_{0 \rightarrow last}$, $AUC_{0 \rightarrow \infty}$, λ_z , $t_{1/2}$ were calculated for each treatment arm. Estimates of treatment differences and 90% confidence intervals were derived.

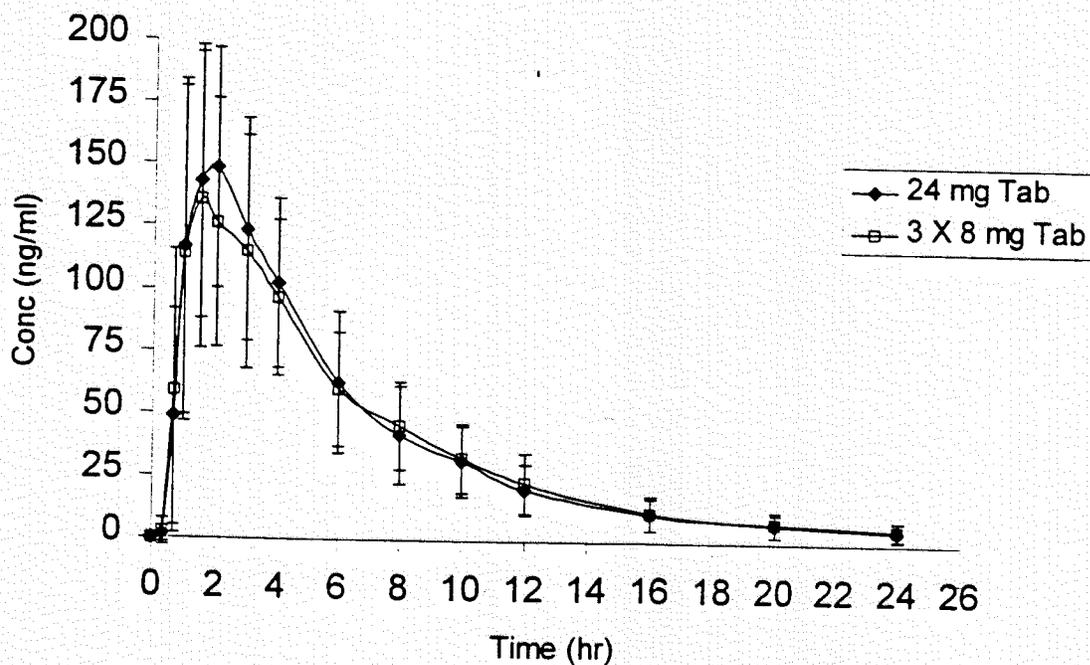


Fig. 1. Mean concentration-time profiles for serum ondansetron (n = 16)

The mean serum concentration-time profiles of ondansetron were closely comparable after single-dose administration of either one 24 mg Zofran tablet or 3 Zofran 8mg tablets (see Fig. 1.). A summary of the statistical analysis of pharmacokinetic parameters for serum ondansetron for both formulations is provided in table 3.

Table 3. Statistical analysis of log-transformed mean ondansetron PK parameters

PK VARIABLE	ESTIMATE TEST/REFERENCE	90% CONFIDENCE INTERVAL
AUC _{0→∞}	1.00	0.98-1.12
AUC _{0→last}	Not Specified	0.98-1.11
C _{max}	1.05	1.00-1.18

The fraction of AUC_{0→∞} attributable to extrapolation was no more than 4-5% of the AUC and no single value exceeded 19%. Analysis of the pharmacokinetic data indicates that the pharmacokinetics of the 24 mg ondansetron tablet is bioequivalent relative to the 3 X 8 mg Zofran tablets (90% confidence intervals for AUC_{0→∞}, AUC_{0→last} and C_{max} are within 0.80-1.25).

Recommendations

Glaxo Wellcome Inc. submitted a clinical bioequivalence study (S3AA1002) along with three clinical studies (S3AA3012, S3AA3004/3007 and S3AA3008) demonstrating safety and efficacy of single-dose 24 mg ondansetron tablets. The Firm seeks to register a 24 mg Zofran tablet for single-dose administration for the prevention of nausea and vomiting associated with highly-emetogenic chemotherapy, including cisplatin. The submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable.

/s/

8/20/99

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader 8/18/1999

FT initialed by David Lee, Ph.D., Team leader

8/20/99

cc: HFD-180: NDA 20,103 (1x); DIV FILE (1x); MMcNEIL (1x); DLEE (1x); SALFAYOUMI (1x);
HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

Table 1. Composition of Zofran tablet core formulations

Product	Zofran tablets (4 mg) (commercial)	Zofran tablets (8 mg) (commercial)	Zofran tablets (24 mg) (development)	Zofran tablets (24 mg) (commercial)
Component	Quantity/dosage unit (mg/tablet)	Quantity/dosage unit (mg/tablet)	Quantity/dosage unit (mg/tablet)	Quantity/dosage unit (mg/tablet)
Ondansetron HCl dihydrate				
lactose				
Microcrystalline cellulose				
Pregelatinized starch				
Magnesium stearate				
Weight				

Table 2. Summary of Zofran controlled clinical studies

PROTOCOL #	COUNTRY	STUDY DESIGN	TREATMENT DOSES	DURATION OF TREATMENT	NUMBER TREATED	AGE RANGE	M/F
S3AA3012	Mexico, Puerto Rico, USA	Randomized, double-blind, parallel, cisplatin (≥ 50 mg/m ²)	Zofran: 8 mg BID po 24 mg QD po 32 mg QD po	24 hr study period	357	13-85	68/32
S3AA3004/ 3007	USA	Randomized, double-blind, parallel, cisplatin (≥ 50 mg/m ² -75 mg/m ²) or carboplatin (≥ 200 mg/m ²)	Zofran: 24 mg QD po Kytril: 10 μ g/kg iv	Single dose, 24 hr study period	371	32-86	56/44
S3AA3008	Canada, France, Germany, Iceland, Italy, Poland, South Africa, UK	Randomized, double-blind, cisplatin (≥ 50 mg/m ²)	Zofran: 24 mg QD po + dexamethasone 12 mg po Zofran: 8 mg QD iv + dexamethasone 20 mg po	Single dose, 24 hr study period	530 (+ 8 subjects who received both treatments)	19-86	61/39

APPENDIX

TABLE 2

SUMMARY OF DERIVED PHARMACOKINETIC PARAMETERS

	Production Formulation	Clinical Trials Formulation
C_{max} (ng/mL)	37.1 (33.2, 41.4)	35.4 (31.7, 39.4)
t_{max} (h)	1.0 (0.67, 2.0)	1.0 (0.67, 2.0)
λ_z (h ⁻¹)	0.17784 (0.17004, 0.18564)	0.17505 (0.16726, 0.18285)
$t_{1/2}$ (h)	3.90 (3.73, 4.08)	3.96 (3.79, 4.14)
$AUC_{0-\infty}$ (ng·h/mL)	192.6 (176.0, 210.7)	192.0 (175.5, 210.1)

C_{max} and $AUC_{0-\infty}$ are shown as geometric means, λ_z as an arithmetic mean and $t_{1/2}$ as a harmonic mean, all with 95% confidence intervals in parentheses. t_{max} is shown as the median with the range in parentheses.

TABLE 3

(SE1/015, 4/20/99)

TREATMENT COMPARISONS

	Estimate	90% CI	p-value
C_{max}	1.05	0.92, 1.19	0.527
$AUC_{0-\infty}$	1.00	0.90, 1.11	0.960
λ_z	0.00279	-0.00634, 0.01192	0.606
t_{max}	0.17	0, 0.17	0.266

The comparisons for C_{max} and $AUC_{0-\infty}$ are based on logarithmically transformed data and are therefore expressed as ratios. Those for λ_z and t_{max} are based on untransformed data and are absolute differences.

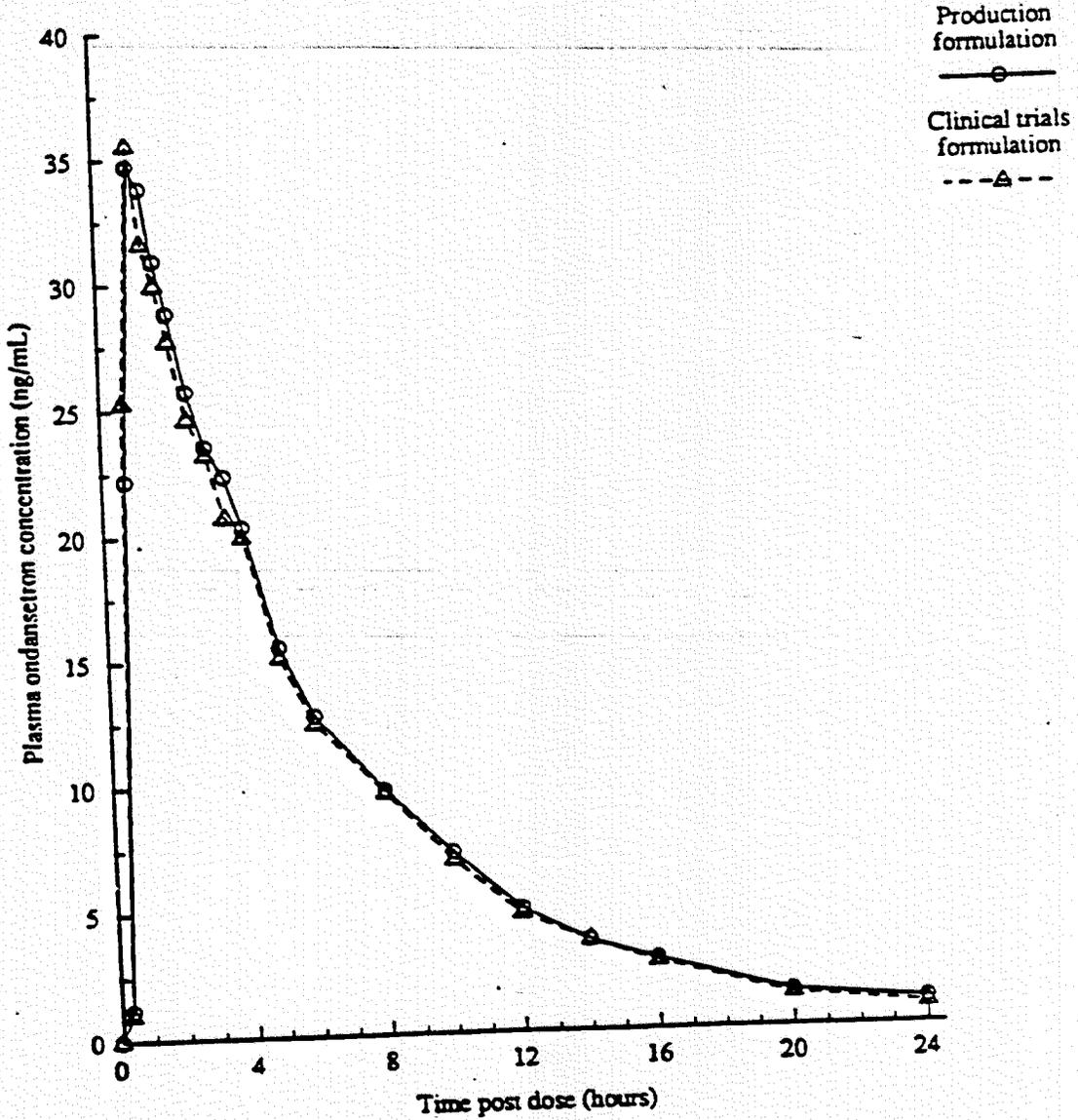
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FIGURES

FIGURE 1

MEAN PLASMA ONDANSETRON CONCENTRATIONS (LINEAR PLOT)

BEST POSSIBLE



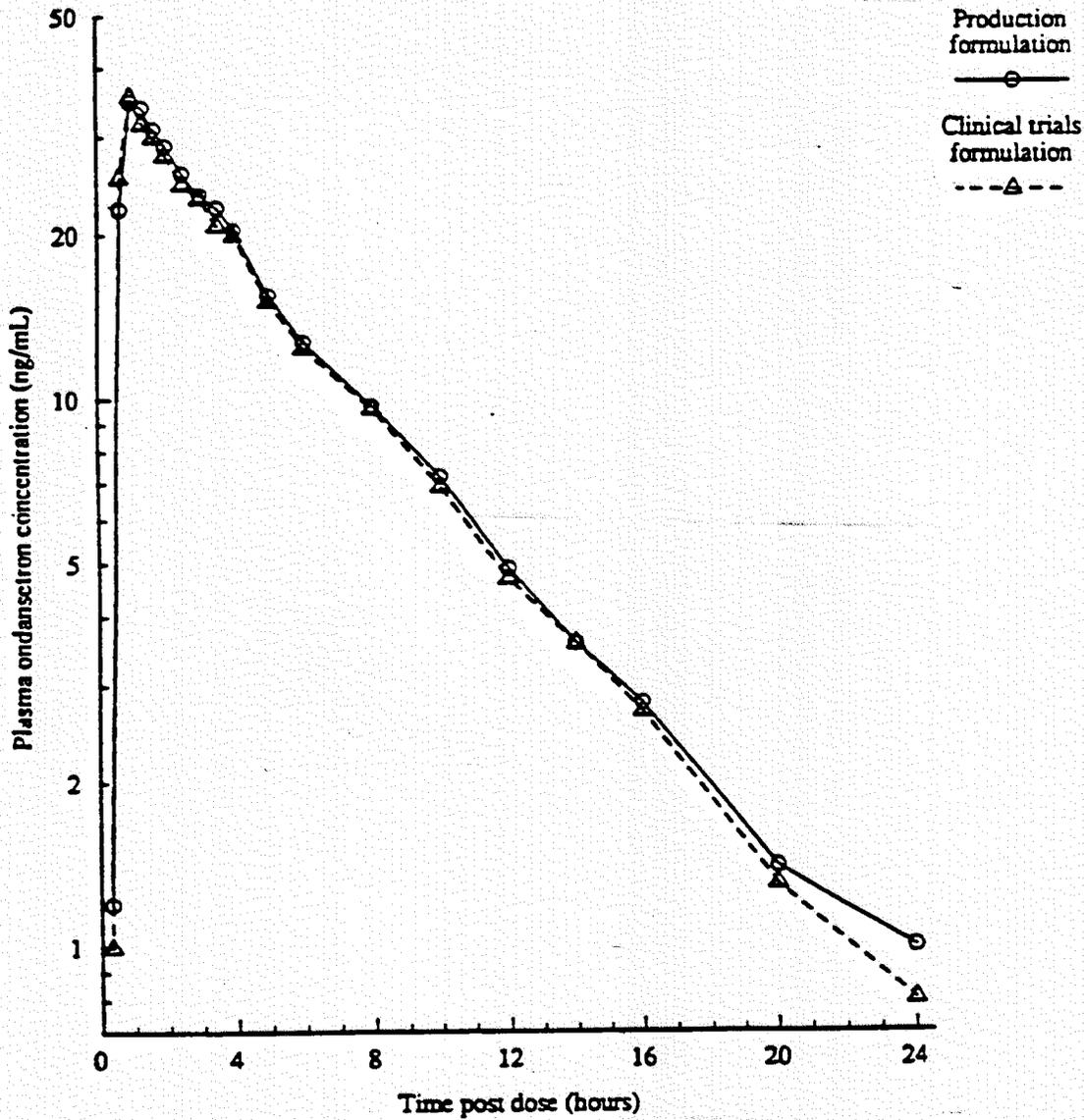
8 mg Zofran Tab.

(SE1/015, 4/20/99)

FIGURE 2

MEAN PLASMA ONDANSETRON CONCENTRATIONS (SEMI-LOGARITHMIC PLOT)

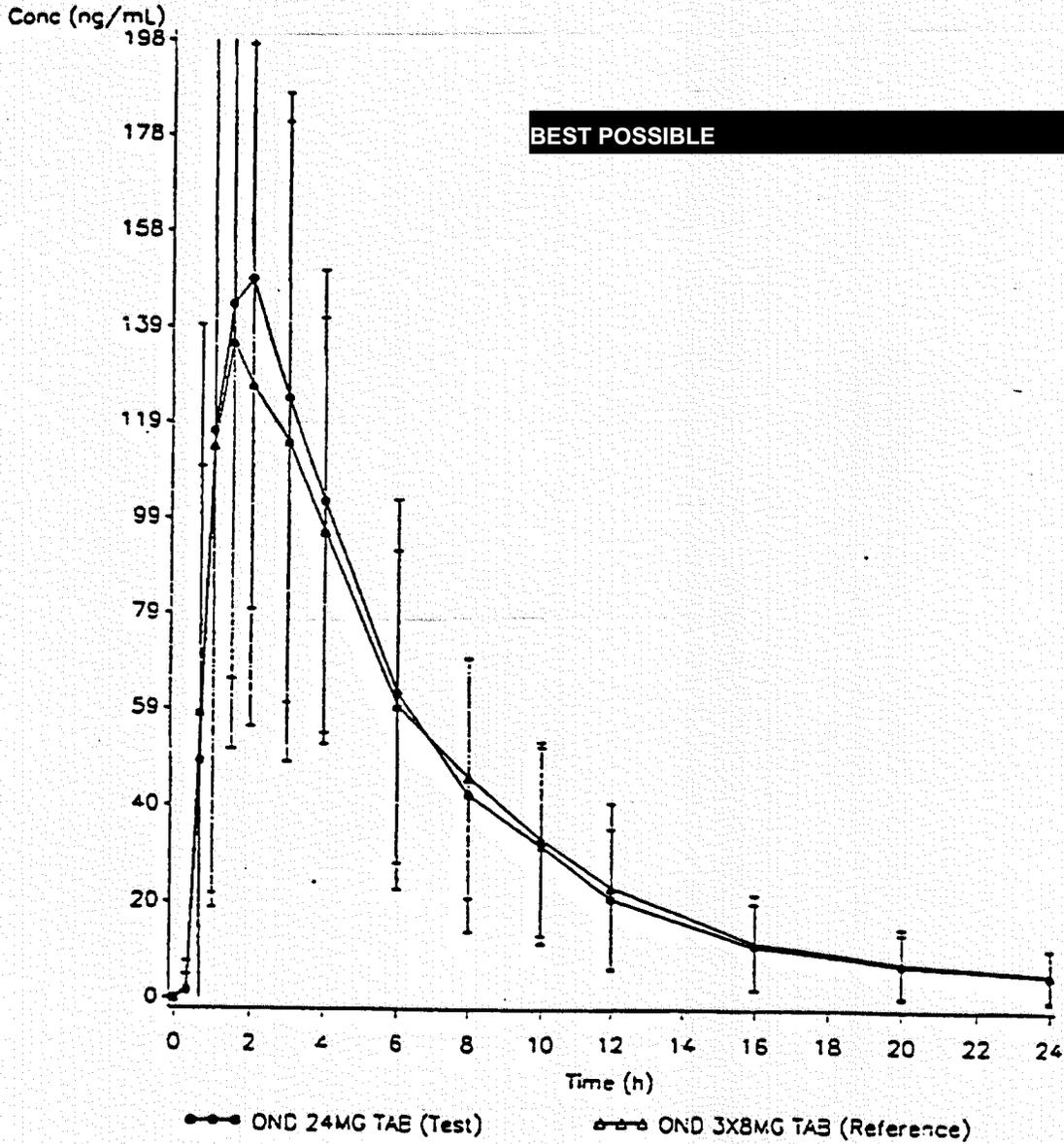
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S3AA1002

(SE1/015, 8/27/99)

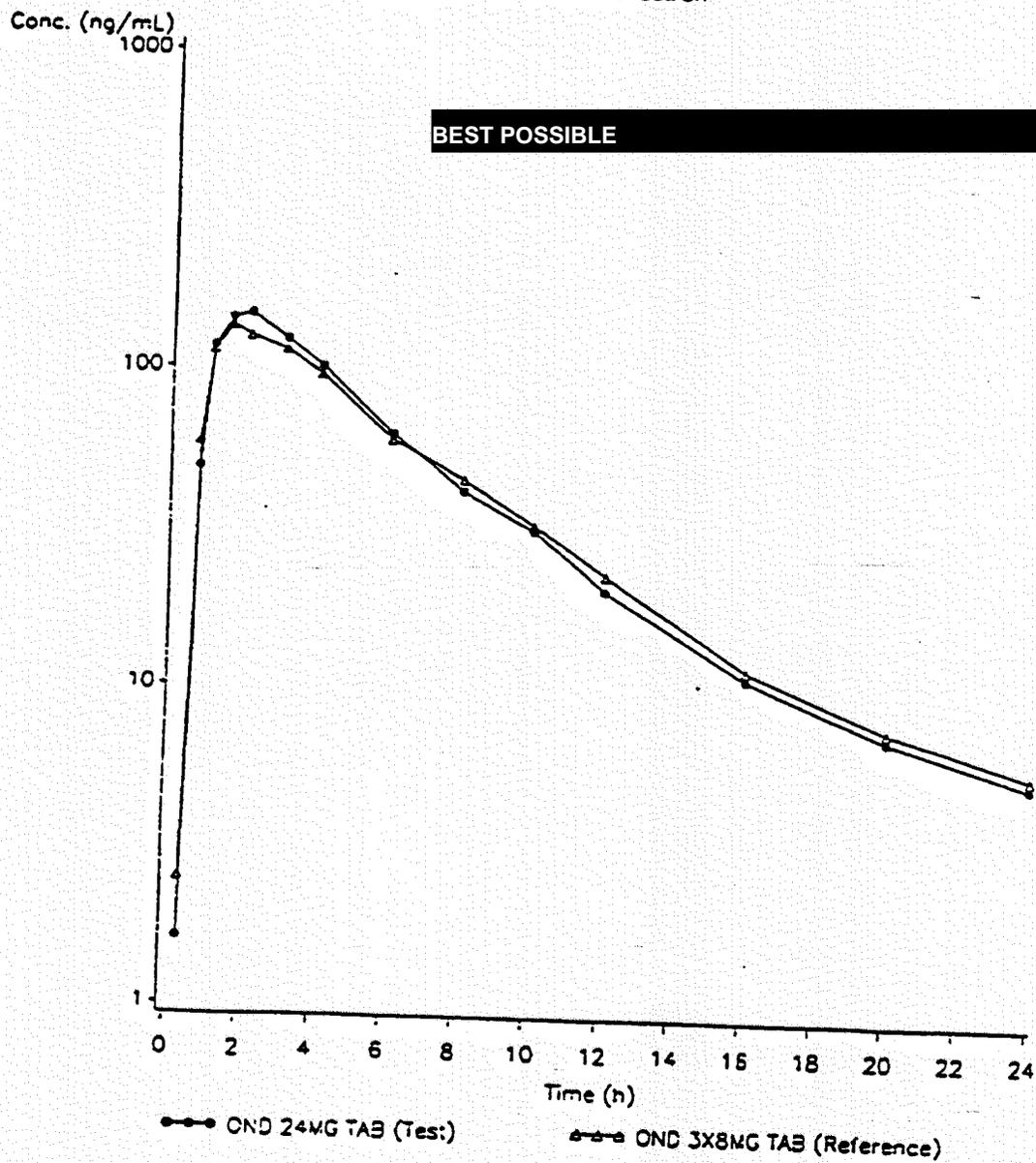
Comparative linear plot of the mean concentration-time profiles (S.D.) for serum ondansetron



S3AA1002

(SE1/015, 8/27/99)

Comparative semi-logarithmic plot of the mean concentration-time profiles for serum ondansetron



S3AA1002

(SE1/015, 8/27/99)

Mean Serum Ondansetron Concentrations with Standard Deviations and Range
(n=16)

Time (h)	OND 24MG TAB (Test)			OND 3x8MG TAB (Reference)		
	Mean	SD	Range	Mean	SD	Range
Pre-dose	0.00	0.00	BLQ - BLQ	0.00	0.00	BLQ - BLQ
0.33	1.61	3.32	BLQ - 12.47	2.50	5.20	BLQ - 16.87
0.67	48.65	43.11	1.12 - 144.51	58.73	56.78	BLQ - 193.60
1.00	118.88	67.37	18.85 - 229.96	113.92	67.29	13.55 - 275.09
1.50	143.15	54.86	70.80 - 249.35	135.59	59.70	45.18 - 254.21
2.00	148.37	48.34	89.54 - 241.60	126.48	50.02	49.33 - 260.67
3.00	123.82	44.62	63.04 - 226.40	114.90	46.81	39.37 - 195.98
4.00	102.45	33.83	51.21 - 183.29	96.37	31.25	35.69 - 150.87
6.00	62.72	28.40	BLQ - 104.99	80.13	22.74	13.93 - 105.25
8.00	41.83	19.76	16.01 - 80.98	45.46	17.47	8.23 - 80.20
10.00	31.57	14.20	7.79 - 61.15	32.89	13.94	6.10 - 54.44
12.00	20.76	10.07	5.19 - 43.00	23.16	12.08	2.05 - 41.88
16.00	11.16	6.23	2.18 - 26.41	11.90	6.91	1.19 - 23.77
20.00	7.26	4.59	1.18 - 17.47	7.76	5.16	BLQ - 17.30
24.00	5.33	3.87	BLQ - 12.97	5.68	3.81	BLQ - 12.17

values below quantifiable limit were set to zero
mean = arithmetic mean
SD = standard deviation

BEST POSSIBLE

S 3 A A 1 0 0 2

(SE1/015, 8/27/99)

Individual Serum Ondansetron Concentrations (ng/mL)

OND 24MG TAB (Test)

Time(h)	Subject 18957	Subject 18958	Subject 18959	Subject 18960	Subject 18961	Subject 18962	Subject 18963	Subject 18964
0.00								
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

OND 1X8MG TAB (Reference)

Time(h)	Subject 18957	Subject 18958	Subject 18959	Subject 18960	Subject 18961	Subject 18962	Subject 18963	Subject 18964
0.00								
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

NR = sample value not reportable or missing
BQL = Below quantitation limit (1.00ng/mL)

S 3 AA 1002

(SE1/015, 8/27/99)

Individual Serum Ondansetron Concentrations (ng/mL)

OND 24MG TAB (Test)

Time(h)	Subject 18965	Subject 18966	Subject 18967	Subject 18968	Subject 18969	Subject 18970	Subject 18971	Subject 18972
0.00								
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

OND 12MG TAB (Reference)

Time(h)	Subject 18965	Subject 18966	Subject 18967	Subject 18968	Subject 18969	Subject 18970	Subject 18971	Subject 18972
0.00								
0.33								
0.67								
1.00								
1.50								
2.00								
3.00								
4.00								
6.00								
8.00								
10.00								
12.00								
16.00								
20.00								
24.00								

NR = sample value not reportable or missing
BQL = Below quantitation limit (1.00ng/mL)