

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-780

STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #: 21-780
DRUG NAME: Nitroglycerin Lingual Spray 0.4 mg
INDICATION: Acute relieve of an attack or acute prophylaxis of angina pectoris due to coronary artery disease
APPLICANT: Novadel Pharma Inc.
DATE OF RECEIPT: July 17, 2004
REVIEW PRIORITY: S
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

NovalDel aerosol nitroglycerin lingual spray (GTN-S) significantly increased the exercise treadmill time (ETT) to the development of moderate angina for the patients who had evidence of coronary artery disease (CAD). However, we should notice that only 1 patient was female (i.e. 3.3% of all patients). In addition, all 30 patients were Caucasians. Generalizability of the single center trial results can be of concern. Statistical significance cannot be assessed for any of the secondary endpoints.

1.2 Brief Overview of Clinical Studies

The sponsor's clinical program of GTN-S included a single center, double-blind, randomized, four-way crossover, dose-ranging, placebo-controlled trial in 30 patients with nitrate-responsive stable angina. These subjects with documented stable angina were assigned to four treatment sequences consisted of four treatment periods with various doses of nitroglycerin lingual spray (0.2mg, 0.4mg, and 0.8mg) and placebo lingual spray. Exercise tests were conducted on 2 study days (2 treatment/day) separated by 1 to 10 days. Exercise testing began 5 minutes after each lingual spray and there was a washout period of approximately 2 hours between administrations of sprays performed on the same day. The primary efficacy parameter is the ETT to development of moderate angina. Moderate angina was defined as severity of chest pain that would normally result in the subject stopping activity. The sponsor is seeking indication that GTN-S doses delay the development of angina.

1.3 Statistical Issues and Findings

In Study FPC 99-003, the primary efficacy endpoint for each of the three GTN-S doses was statistically significantly superior to placebo ($p \leq 0.0003$). In addition, the two higher doses (0.4mg and 0.8mg) GTN-S were also statistically significantly better than the lowest dose level, 0.2mg, ($p=0.0095$ and $p=0.0004$, respectively). However, there is no statistically significant difference between 0.4mg and 0.8mg GTN-S dose. Generalizability from single-center results can be of concern. No statistical significance criterion was pre-specified in the protocol for the secondary endpoints. Thus, statistical significance cannot be concluded for these endpoints.

2. INTRODUCTION

2.1 Overview

Aerosol nitroglycerin lingual spray (GTN-S) is intended to prevent the spread and acute relief of angina pectoris due to CAD. In this submission, the sponsor conducted a one-dose-ranging study (FPC 99-003) to support demonstrate the efficacy and safety of GTN-S. The study was conducted at 3 dosage levels (0.2, 0.4, and 0.8 mg per spray) compared to a placebo lingual spray in 30 patients with documented stable angina who are considered to be nitrate responders. There

was a definitive PK study (Study 131-63-11700) provided safety data on a higher dose of 1.2 mg GTN-S, but it was not designed as a pivotal clinical study. Therefore, this review only focuses on the evaluation of efficacy for Study FPC 99-003.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\CDSESUB1\N21780\N_000\2004-07-29 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The study description in this section is based on the sponsor's study report.

3.1.1 STUDY OBJECTIVES

The objective of study FPC 99-003 was to assess the anti-anginal efficacy of a new, aerosol nitroglycerin lingual spray (GTN-S) at three dosage levels (0.2 mg, 0.4 mg, 0.8 mg) compared to a placebo lingual spray.

3.1.2 STUDY DESIGN

This study was a single center, double-blind, randomized, four-way crossover, dose-ranging, placebo-controlled trial in 30 patients with nitrate-responsive stable angina. The study population consists of subjects with documented stable angina who met eligibility criteria and considered to be nitrate responders. Before randomization, subjects were asked to perform a treadmill exercises test ("screening" test). A second test was then carried out after administration of 0.4mg GTN-S to determine whether subjects were to be considered to be nitrate responders. Finally, the patients who had showed reproducible exercise time as compared to the screening test were randomly allocated to one of the following treatment sequences in four treatment periods:

Sequence 1: A, B, C, D

Sequence 2: B, C, D, A

Sequence 3: C, D, A, B

Sequence 4: D, A, B, C

A = GTN-S 0.2 mg, B = GTN-S 0.4 mg, C = GTN-S 0.8 mg, D = placebo.

3.1.3 EFFICACY MEASURES

(1) Primary Efficacy Endpoint

The primary efficacy variable was change in exercise time to development of moderate angina from baseline to endpoint (CHANTIME).

(2) Secondary Efficacy Endpoints

The following are the secondary efficacy variables:

- Time to onset of first symptoms of angina
- Reason to discontinue exercise (angina vs. all other reasons combined)
- Changes in efficacy parameters (heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, pressure rate product) from standing measurement after dosing to the development of moderate angina
- Changes in efficacy parameters (heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, pressure rate product) from standing measurement before dosing to the development of moderate angina
- Changes in efficacy parameters (heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, pressure rate product) from standing measurement after dosing to onset of the first symptoms of angina
- Time to development of 1mm of ST-segment depression

3.1.4 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Table 1 is the summaries of the patient participation, demographic and baseline characteristics for Study FPC 99-003. Everybody completed the study in each treatment group of the study.

Table 1. Patient Participation, Demographic and Baseline Characteristic

	Total N=30
Disposition N(%)	
Completed	30 (100.0)
Incomplete	0 (0.0)
Demographic Characteristics	
Sex N(%)	
Male	29 (96.7)
Female	1 (3.3)
Age Mean (SD) Years	66.5 (8.8)
Ethnicity N(%)	
Caucasian	30 (100.0)
Other	0 (0.0)
Baseline Time to Stopping Exercise	
N	30
Mean	4.60
SD	1.28
Median	4.36
Range	2.53 – 7.60

[Source: Reviewer's analysis]

3.1.5 STATISTICAL METHODOLOGIES

3.1.5.1 Sponsor's Primary Efficacy Results

The primary efficacy variable was change in exercise treadmill times (minutes) to development of moderate angina from baseline to endpoint. Increase in the exercise time indicates improvement. The primary analysis results are summarized in Table 2. According to the sponsor, the primary efficacy analysis for all three GTN-S doses were statistically significantly superior compared to placebo ($p \leq 0.0003$). In addition, 0.4mg and 0.8mg GTN-S dose were also statistically significantly better than 0.2mg dose ($p=0.0095$ and $p=0.0004$, respectively). However, there is no statistically significant difference between 0.4mg and 0.8mg GTN-S dose.

Table 2. Mean change in ETT to development of moderate angina from baseline to endpoint

	Placebo	GTN-S		
		0.2 mg	0.4 mg	0.8 mg
N	30	30	30	30
Mean at baseline	4.60	4.60	4.60	4.60
Mean at endpoint	5.30	5.81	6.16	6.30
LS mean change (SE)	0.69 (0.10)	1.20 (0.10)	1.56 (0.10)	1.70 (0.10)
Percent change relative to placebo LS mean change	-----	74%	126%	146%
p-value ¹	-----	0.0003	0.0001	0.0001
p-value ²	-----	0.0004	0.30	-----
p-value ³	-----	0.0095	-----	-----

[Source: Sponsor's Table 2.8.2, page 57, Volume 1.1, green jacket document; confirmed by reviewer's analysis]

GTN-S = nitroglycerin Lingual Spray LS = least squares

Baseline was defined as exercise treadmill time to development of moderate angina during the screening phase.

Endpoint was defined as exercise treadmill time to development of moderate angina during the double-blind phase

Statistical comparisons were based on ANOVA model with sequence, subject within sequence, period, and treatment. P-values correspond to the differences in change (endpoint minus baseline) between treatments.

¹ p-value for comparisons of nitroglycerin versus placebo

² p-value for comparison of 0.8 mg versus 0.2 mg and 0.4 mg

³ p-value for comparison of 0.4 mg versus 0.2 mg

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Table 3 presents the mean change in exercise treadmill time from baseline in every period of every sequence. There was no evidence of treatment by sequence interaction or differential carryover effect. Therefore, the analyses in Table 2 are statistically valid for the pairwise treatment comparisons.

Table 3. Mean change in ETT to development of moderate angina from baseline to endpoint by period by sequence

treatment/ mean change	Period 1	Period 2	Period 3	Period 4
Sequence 1 (n=7)	A / 1.02	B / 1.23	C / 1.54	D / 0.77
Sequence 2 (n=8)	B / 1.65	C / 1.48	D / 0.78	A / 1.17
Sequence 3 (n=8)	C / 1.64	D / 0.68	A / 1.24	B / 1.58
Sequence 4 (n=7)	D / 0.52	A / 1.40	B / 1.76	C / 2.15

[Source: Reviewer's analysis]

A = GTN-S 0.2 mg B = GTN-S 0.4 mg C = GTN-S 0.8 mg D = placebo

Also note that Table 3 showed the placebo group had a mild increase over Period. However, such result is not observed for other three treatment groups. This phenomena may be explained by the training effect which in favored placebo.

Sponsor's Secondary Efficacy Results

The changes relative to baseline in selected secondary efficacy measurements for all four treatments are listed in the Table 4. According to the sponsor, the mean changes in standing HR and SBP from before dosing to after dosing were statistically significantly in favor of GTN doses ($p < 0.05$). The sponsor made the similar claims for the mean changes in standing SBP and RPP from after dosing to development of moderate angina and the mean change in standing SBP from after dosing to the first onset of angina.

Table 4. Comparative Secondary Efficacy Evaluation of Three Doses of GTN spray

Parameters	Placebo	GTN-S		
		0.2mg	0.4mg	0.8mg
Mean change in ETT to First Onset of Angina from Baseline to Endpoint	0.57	0.88	1.30	1.26
Mean change in Standing HR from before dosing to after dosing	7.64	12.99	15.73	18.31
Mean change in Standing SBP from before dosing to after dosing	-6.16	-15.58	-20.96	-24.14
Mean change in Standing DBP from before dosing to after dosing	0.16	-3.68	-2.08	-1.91
Mean change in Standing RPP from before dosing to after dosing	6.01	5.97	4.83	4.16
Mean change in Standing HR from after dosing to Development of Moderate Angina	45.50	46.00	44.55	42.44
Mean change in Standing SBP from after	34.72	49.29	56.13	60.62

dosing to Development of Moderate Angina				
Mean change in Standing DBP from after dosing to Development of Moderate Angina	4.46	8.20	6.65	6.87
Mean change in Standing RPP from after dosing to Development of Moderate Angina	98.83	113.80	120.25	122.54
Mean change in Standing HR from after dosing to the First Onset of Angina	37.67	37.14	35.91	33.58
Mean change in Standing SBP from after dosing to the First Onset of Angina	30.49	42.26	48.44	55.58
Mean change in Standing DBP from after dosing to the First Onset of Angina	2.04	7.42	5.84	5.43
Mean change in Standing RPP from after dosing to the First Onset of Angina	81.46	91.25	97.46	101.75
Median Time to Development of 1-mm ST-segment depression	4.78	5.83	5.02	5.83

[Source: Sponsor's Table 2.8.3, page 59, Volume 1.1, green jacket document; mostly confirmed reviewer's analysis, except bold – Italic font numbers.]

DBP=diastolic blood pressure; ETT= exercise treadmill time; GTN-S=glycerol trinitrate (nitroglycerin) lingual spray; HR=heart rate; RPP=rate-pressure product; SBP=systolic blood pressure.

3.1.6 RESULTS AND CONCLUSIONS

Tables 2 and 4 present the results for the analysis of the primary endpoint and secondary endpoints in the study FPC 99-003.

1. This reviewer confirmed the sponsor's efficacy analysis results for primary endpoint. No inconsistent finding was found.
2. For some secondary endpoints, this reviewer could not replicate the sponsor's Table 2.8.3 from page 59 of Volume 1.1. The discrepancies are displayed as Italic-Bold font in Table 4. In addition, there was no pre-specified statistical significance criterion for the secondary endpoints. No multiple-comparison procedure is mentioned in the protocol for the secondary efficacy parameters. Therefore, in our review, no significance claims for any of these secondary endpoints can be made in favor of nitroglycerin lingual spray.

3.2 Evaluation of Safety

Please read Dr. Williams's review for safety assessment.

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