

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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MEDICAL REVIEW

NITROGLYCERIN LINGUAL SPRAY CLINICAL REVIEW

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Established Name Nitroglycerin
(Proposed) Trade Name Aerosol Nitroglycerin Lingual Spray
Therapeutic Class Nitrates
Applicant NovaDel Pharma, Inc.

Priority Designation S

Formulation Aerosol Spray

Dosing Regimen 3 sprays of aerosol nitroglycerin lingual
spray (0.2, 0.4 and 0.8mg per activation). One dose of 3 sprays of 0.4mg each.

Indication Angina Pectoris

Intended Population Patients with chronic stable angina
considered to be nitrate responders.

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1. Executive Summary

This was a single center, placebo-controlled, double-blind, randomized, 4-way, crossover study of nitroglycerine spray using butane as a propellant (instead of CFC) in patients with chronic stable angina pectoris and coronary artery disease. The oral spray is a form of delivery modality that has been in use for more than 20 years. This modality provides greater stability compared to the sublingual tablets because the spray is a lipid solution in a metal container that is administered by metered dose. In contrast, repeated opening of a bottle of sublingual nitroglycerine tablets predisposes to chemical breakdown of glyceryl trinitrate to less active compounds by exposure to heat, light, and moisture.

The primary objective of this study is to assess the anti-anginal efficacy of a new aerosol nitroglycerin lingual spray at 3 dosage levels (0.2, 0.4, 0.8 mg per activation) compared to a placebo lingual spray. The study compared 3 sprays (0.2, 0.4, 0.8 mg per activation) with placebo lingual spray in 30 patients with documented stable angina who were considered to be nitrate responders. The study was completed on 12/13/2002. One dose shall be up to 3 sprays of 0.4 mg per activation making a total of 1.2 mg. (See dosage and administration section).

Results:

- The results of the study suggest that 0.2, 0.4, and 0.8 mg nitroglycerin administered as a lingual spray in subjects with stable angina was efficacious (Tables 3 and 4, Figure 1) and safe.
- The 0.4 mg dose was significantly better than the 0.2 mg dose.
- The 0.8 mg dose was not statistically significantly better than 0.4mg and showed no significant clinical benefit over the 0.4 mg dose.
- Of the three doses used, the two doses that provided clinical benefit were 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate for commercial dosing.
- No patients died during the study.
- Nine of the 30 subjects exposed to the study drug in the protocol experienced at least one adverse event.
- A total of 16 mild adverse events were reported during the study and in the safety update (Table 6 and IND 64596).
- A pilot PK study of the spray at 0.4 mg per activation under fasting conditions (study FPC 99-003) demonstrated that NovaDel GTN-S produced blood levels of GTN, 1,2-GDN and 1,3-GDN in all subjects in the study and that the PK parameters for all three were within the historic range found for other lingual sprays and oral formulations reported in the literature.
- Pharmacodynamic data showed that nitroglycerin lingual spray at 0.4 and 0.8 mg per activation had an anti-anginal effect demonstrated by clinically and statistically significant increases in time to 1 mm ST segment depression when compared to placebo spray ($p \leq 0.0467$). This prolongation in time, however, was not dose dependent as there was no difference between the 0.4 and the 0.8 mg dose levels ($p = 0.3036$) (Table 5).

The data from this NovaDel-sponsored single study suggest that treatment of patients with chronic stable angina with aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation) results in increase time from start of exercise to development of moderate angina in men (only one female) compared to placebo. The sponsor cannot claim that this happened in females based on one female and a single NovaDel-sponsored trial of 30 subjects. Furthermore, aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation), in a dose dependent manner, results in increased time to first onset of angina and in time to 1 mm ST segment depression suggesting an anti-anginal affect based on an anti-ischemic effect. At rest, the expected dose related nitrate effects on heart rates and blood pressure were observed. The ability of subjects to exercise to a higher rate-pressure product provides further support for efficacy. The spray was well tolerated based on the relative ratio- frequencies (RRF) of common adverse events and the relative lack of serious adverse events.

Protocol: Study design

The study was randomized, double-blind, four-way crossover dose-ranging, and placebo-controlled. Prior to randomization there was screening using a treadmill exercise test.

Inclusion Criteria

Subject must be male or female, aged ≥ 21 years

Subject had chronic stable angina pectoris of at least 1 month's duration documented by at least one of the following:

- History of MI confirmed by ECG or enzyme change.
- Coronary angiography abnormalities with $>60\%$ narrowing of one of the major pericardial arteries.
- Positive myocardial perfusion scan, positive stress echo, or positive dobutamine stress Echo.
- Male subjects with classical angina pectoris with a positive ETT.

Exclusion criteria

- Subjects with any of the following criteria:
- Subject had MI, coronary angioplasty, stent implantation or bypass surgery within 2 months of screening within 2 months of screening.
- Subject had unstable angina pectoris within 1 month of screening.
- Subject had clinically significant valvular heart disease or other cardiac conditions with chest pains.
- Pregnant subject, nursing or of child bearing potential, and not using an adequate method of birth control.
- History of hypertension (SBP >200 mm Hg, DBP > 10 mmHg).
- Subject with a history of hypotension (SBP < 100 mm Hg).
- Subject has a history of PAD, or pulmonary disease.
- Subject with organic nitrate intolerance.
- Subject with uncontrolled diabetes mellitus.
- Subject with significant laboratory abnormalities.
- Subject had received investigational drugs within 30 days of screening.

Screening: Screening of patients used the Bruce protocol. Subjects who developed angina between 2 and 9 minutes on a treadmill exercise test were eligible to participate in the study.

Sixty minutes after the first exercise test, 0.4 mg of nitroglycerin lingual spray was administered and a second exercise test was conducted 5 minutes later. Patients who improved on their exercise time by 20 percent or by 60 seconds were considered to be nitrate responders and were eligible to continue in the study. Eligibility of subjects was confirmed among those who showed reproducible exercise times as defined in the protocol.

Double blind phase of the study: Thirty patients were randomly assigned to 1 of 4 treatment sequences. Each treatment sequence consisted of 4 treatment periods in a prespecified order. Exercise tests were conducted on 2 study days (2 treatments/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.

Primary efficacy was the exercise treadmill time (ETT) to the development of moderate angina following the administration of 3 sprays of aerosol (0.2, 0.4, 0.8 mg per activation) and placebo lingual spray. Moderate angina was defined as severity of chest pain that would normally result in the subject stopping activity. When angina did not develop within 20 minutes the subjects continued the exercise until symptoms limited the exercise.

Safety evaluation included the collection of adverse events and discontinuation/completion data. Efficacy summaries were based on the I-T-T population defined as the population of randomized patients who received at least 1 dose of the double-blind treatment and at least 1 post-randomization measurement of efficacy was obtained.

The primary measure of efficacy was change in ETT (investigational ETT – control [screening] ETT) to the development of moderate angina following the double blind administration of 3 sprays of aerosol nitroglycerin spray (0.2, 0.4, 0.8 mg) and placebo lingual spray. An analysis of variance (ANOVA) was performed to detect between-different differences in the changes from screening to the double-blind treatment in the primary efficacy variable (ETT).

Proposed Analyses of time points by sponsor

- The following time points were used for statistical analyses:
- Time to onset of moderate angina (Tables 5 and 6 in this review).
- Time of onset of first symptoms of angina (Table 2 in this review)
- Time of efficacy measurements before dosing (Not possible as there cannot be efficacy before dosing)
- Time of efficacy measurements after dosing (Tables 10, 12 and 13 in this review).
- Time of development of 1 mm of ST-segment depression (Tables 9, 14 – 16 in this review).

The results of the analyses listed above are in tables/figures opposite each analysis in parentheses.

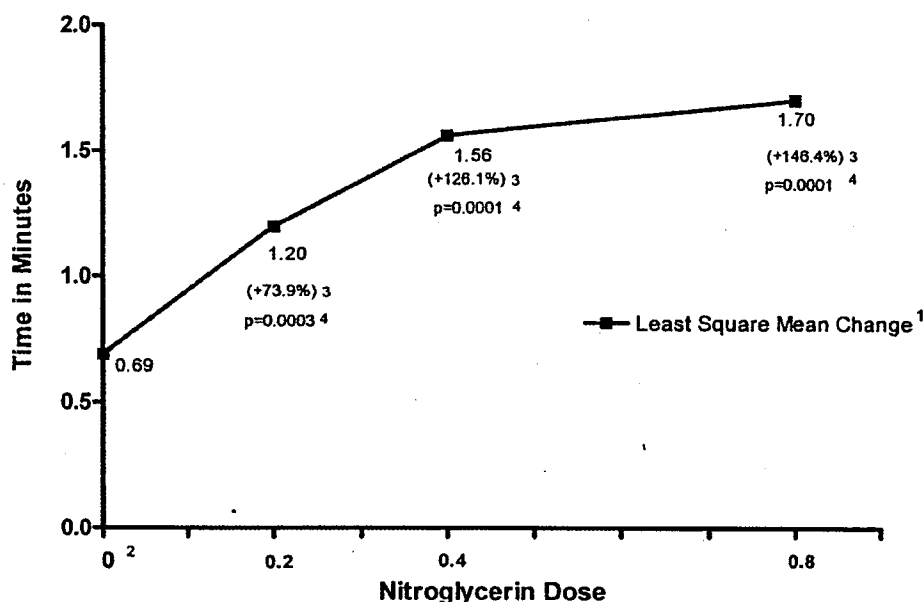
Primary efficacy analyses included comparing: 1) each of the four treatments with no treatment at screening (baseline) for change in ETT to onset of moderate angina and 2) each of the 3 GTN treatments with placebo for differences in the magnitude of this ETT change. This approach was

used to evaluate treatment differences for changes in all the secondary efficacy parameters (Tables 7-9, 17 in this review).

Efficacy - Primary

An overall treatment effect on the mean changes in exercise time to development of moderate angina was highly significant ($p=0.0001$) (Table 6). The scatter gram of individual data points of time from start of exercise to onset of angina is presented in Figure 2. This does not show any significant outliers in any of the treatment groups. The percent change in exercise time in minutes to development of moderate angina relative to placebo is presented in Figure 2. For each of the doses there is a greater than 20% increase that supports efficacy. Compared with placebo, all 3 nitroglycerin dose levels showed significantly prolonged ETT to development of moderate angina ($p\leq 0.0003$) (Table 5; Figures 3 and 4). Both the 0.4 mg and 0.8 mg dose levels were significantly better in prolonging ETT when compared with the 0.2 mg dose level ($p=0.0095$ and $p=0.0004$, respectively) (Table 5). However, there was no statistically significant difference in ETT between the 0.4 and 0.8 mg dose levels ($p=0.3036$) (Table 5). A clear dose response relationship was also observed for prolonging the time to development of moderate angina with mean changes of 1.20, 1.56, and 1.70 minutes in subjects receiving 0.2, 0.4, 0.8 mg nitroglycerin, respectively (Figures 1, 3 and 4). For each dose of 0.2, 0.4 and 0.8 mg nitroglycerin spray, the increase from baseline in mean time to onset of moderate angina was greater than 20% when compared with placebo spray, a further support for efficacy (Figure 1).

Figure 1: Changes in ETT (minutes) to development of Moderate Angina from baseline



- 1 Least square mean change for the difference: Investigational Drug ETT – Control (Screening) ETT.
- 2 0 mg represents placebo treatment group.
- 3 Percent change relative to placebo least square mean change.
- 4 P-value for the comparisons of nitroglycerin treatment groups versus placebo.

Conclusions: Primary efficacy

- An overall treatment effect on the time to development of moderate angina was highly statistically significant ($p=0.0001$).
- Nitroglycerin lingual spray (0.2, 0.4, 0.8 mg per activation) resulted in increase in exercise time to first onset of angina as compared to placebo.
- In addition, to prolonging the ETT, and time to first onset of angina, nitroglycerin lingual spray demonstrated statistically significant increases in time to 1 mm ST segment depression for the 0.4, and 0.8 mg nitroglycerin doses when compared to placebo spray ($p \leq 0.0003$; log rank test) during the dosing period suggesting that the anti-anginal effect of the nitroglycerin may be based and anti-ischemic effect.
- Before starting the treadmill exercise, effects on hemodynamic endpoints expected of nitrates, namely, increase heart rate and systolic blood pressure as compared to placebo, were observed.

Secondary Efficacy

Secondary efficacy measurements included the following:

- ETT to first onset of angina (Table 13).
- Reason to discontinue treadmill exercise (Table 3).
- Resting standing, changes and exercise induced heart rate (HR),

- systolic and diastolic BP, SBP, DBP, and RPP (Table 8)
- time to development of 1 mm ST-segment depression (Table 9)
- Changes in ST segment depression measurements.

Conclusions: Secondary efficacy

The data in support of secondary efficacy are in Tables 14-17 and figures 6-9

- An overall treatment effect on the time to first onset of angina was highly statistically significant ($p=0.0007$) (Table 13)
- The 0.4 and 0.8 mg nitroglycerin doses were statistically significantly better compared to placebo ($p\leq 0.0008$) whereas 0.2 mg was not ($p=0.1081$) (Table 13).
- The 0.4 mg was significantly better compared to 0.2 mg ($p=0.0364$) (Table 13).
- The changes with 0.2 and 0.4 mg nitroglycerin doses were not significantly different from that with the 0.8 mg ($p=0.0678$ and 0.8180) (Table 13).
- Dose-related effects on hemodynamic endpoints at rest showed statistically significant differences consistent with nitrate effects.
- Each of the nitroglycerin dose produced clinically meaningful and highly significant increases in heart rates with mean changes of 12.99, 15.73 and 18.31 beats per minute in subjects receiving 0.2 0.4 and 0.8 mg nitroglycerine, respectively, as compared to placebo (7.65 beats /minute) ($p=0.0001$). (Table 17; Figures 6 and 7).
- Each of the nitroglycerin dose produced clinically meaningful and highly significant decreases in systolic blood pressure with mean changes of -15.58, -20.96 and -24.14 mmHg in subjects receiving 0.2 0.4 and 0.8 mg nitroglycerine, respectively, as compared to placebo (-6.16 mmHg) ($p=0.0002$). (Figures 8 and 9 showing LS mean changes).

Safety

Safety data (discontinuations/completion information, adverse events, concomitant medications, etc.,) are summarized in tables derived from listings.

A total of 10 adverse events were reported by 7 (23.3%) patients, all occurring after administration of nitroglycerin spray at end of study. Adverse events were reported by 2/30 (6.7%) patients who received 0.2 mg, 1/30 (3.3%) patients who received 0.4 mg and 7/30 (23.3%) who received 0.8 mg of nitroglycerin. All the adverse events were considered to be possibly or probably related to the drug but none of the events were serious or severe (Table 20). There was no discontinuation. The most common adverse events were headaches (4) and fullness in the head (3). There were no changes from baseline in physical examination findings. Treatment with nitroglycerin lingual spray was well tolerated (Tables 21-22).

In the clinical pharmacology study (PK study- 131-63-11700) of 12 healthy volunteers given a single dose of 1.2 mg GTN-S under fasting conditions following pre-medication with 200 mg ibuprofen, (eleven Caucasians, 1 black, and 11 males), nine of the subjects experienced a total of 16 adverse events. Eleven of these 16 adverse events were judged to be drug related and the most common AE was headache (Table 21).

Summary

This study showed the following:

Nitroglycerin administered as a lingual spray at dose levels of 0.2, 0.4, and 0.8 mg in patients with stable angina appears to be efficacious and safe as an anti-anginal agent.

The 0.4 mg dose was significantly better than the 0.2 mg dose.

The 0.8 mg dose is not statistically significantly better than 0.4mg and shows no significant clinical benefit over the 0.4 mg dose.

Of the three doses, used the most appropriate doses that provide clinical benefit are 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate commercial dose.

Recommendation on Regulatory Action

This reviewer recommends that the sponsor should make additional efforts to study female subjects as only one subject has been studied in this protocol. The lack of females in this study is not in compliance with statutory regulations regarding women's health

However there are data in published literature on females but these are also small numbers.

Recommendation on Postmarketing Actions

1.1.1 Risk Management Activity

This is a very well known drug with considerable safety database. The only difference between this drug and others on the market is the propellant butane. There are several pumps (13) on the market and their safety profiles have been described. It is therefore not necessary to have a post marketing risk management activity. There are no post-marketing studies planned.

1.1.2 Required Phase 4 Commitments

This is a very well known drug with considerable safety database. The only difference between this drug and others on the market is the propellant butane. There are several pumps (13) on the market and their safety profiles are well known. It is therefore not necessary to have a phase 4 study. There is no need for pediatric studies as coronary artery disease is predominantly experienced in adults.

1.1.3 Other Phase 4 Requests

See section 8.

Summary of Clinical Findings

1.1.4 Brief Overview of Clinical Program

This was a single center, placebo-controlled, double-blind, randomized, 4-way, crossover study of nitroglycerine spray using butane as a propellant (instead of CFC) in patients with chronic stable angina pectoris and coronary artery disease. The oral spray is a form of delivery modality that has been in use for more than 20 years. This modality provides greater stability compared to the sublingual tablets because the spray is a lipid solution in a metal container that was administered by metered dose. In contrast, repeated opening of a bottle of sublingual nitroglycerine tablets predisposes to chemical breakdown of glyceryl trinitrate to less active compounds by exposure to heat, light, and moisture.

The primary objective of this study is to assess the anti-anginal efficacy of a new aerosol nitroglycerin lingual spray at 3 dosage levels (0.2, 0.4, 0.8 mg per activation) compared to a placebo lingual spray. The study compared 3 sprays (0.2, 0.4, 0.8 mg per activation) with placebo lingual spray in 30 patients with documented stable angina who were considered to be nitrate responders. The study was completed on 12/13/2002. One dose shall be up to 3 sprays of 0.4 mg per activation making a total of 1.2 mg. (See dosage and administration section).

The primary measure of efficacy was change in ETT (investigational ETT – control [screening] ETT) to the development of moderate angina following the double blind administration of 3 sprays of aerosol nitroglycerin spray (0.2, 0.4, 0.8 mg) and placebo lingual spray. An analysis of variance (ANOVA) was performed to detect between-different differences in the changes from screening to the double-blind treatment in the primary efficacy variable (ETT).

Efficacy

An overall treatment effect on the time to development of moderate angina was highly significant ($p=0.0001$). Compared with placebo, all 3 nitroglycerin dose levels showed significantly prolonged ETT to development of moderate angina ($p\leq 0.0003$). A clear dose

response relationship was also observed for prolonging the time to development of moderate angina. Both the 0.4 mg and 0.8 mg dose levels were significantly better in prolonging ETT when compared with the 0.2 mg dose level ($p=0.0095$ and $p=0.0004$, respectively). However, there was no statistically significant difference between the 0.4 and 0.8 mg dose levels ($p=0.3036$).

Conclusions:

- Nitroglycerin lingual spray (0.2, 0.4, 0.8 mg per activation) resulted in increase in exercise time to first onset of angina as compared to placebo.
- In addition, to prolonging the ETT, and time to first onset of angina, nitroglycerin lingual spray demonstrated statistically significant increases in time to 1 mm ST segment depression for the 0.4, and 0.8 mg nitroglycerin doses when compared to placebo spray ($p\leq 0.0003$; log rank test) during the dosing period suggesting that the anti-anginal effect of the nitroglycerin may be based on an anti-ischemic effect.
- Before starting the treadmill exercise, effects on hemodynamic endpoints expected of nitrates, namely, increase heart rate and systolic blood pressure as compared to placebo, were observed.

Safety

A total of 10 adverse events were reported by 7 (23.3%) patients, all occurring after administration of nitroglycerin spray. Adverse events were reported by 2/30 (6.7%) patients who received 0.2 mg, 1/30 (3.3%) patients who received 0.4 mg and 7/30 (23.3%) who received 0.8 mg of nitroglycerin. All the adverse events were considered to be possibly or probably related to the drug but none of the events were serious or severe. There was no discontinuation. The most common adverse events were headaches (4) and fullness in the head (3). There were no changes from baseline in physical examination findings. Treatment with nitroglycerin lingual spray was well tolerated.

Summary

This study showed the following:

Nitroglycerin administered as a lingual spray at dose levels of 0.2, 0.4, 0.8 mg in patients with stable angina appears to be efficacious and safe as an anti-anginal agent.

The 0.4 mg dose was significantly better than the 0.2 mg dose.

The 0.8 mg dose is not statistically significantly better than 0.4mg and shows no significant clinical benefit over the 0.4 mg dose.

Of the three doses, used the most appropriate doses that provide clinical benefit are 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate commercial dose.

1.1.5 Efficacy

Efficacy-Primary and secondary

An overall treatment effect on the time to development of moderate angina was highly significant ($p=0.0001$). Compared with placebo, all 3 nitroglycerin dose levels showed significantly prolonged ETT to development of moderate angina ($p\leq 0.0003$). A clear dose response relationship was also observed for prolonging the time to development of moderate angina. Both the 0.4 mg and 0.8 mg dose levels were significantly better in prolonging ETT

when compared with the 0.2 mg dose level ($p=0.0095$ and $p=0.0004$, respectively). However there was no statistically significant difference between the 0.4 and 0.8 mg dose levels ($p=0.3036$) (Table 5).

Conclusions

- Nitroglycerin lingual spray (0.2, 0.4, 0.8 mg per activation) resulted in increase in exercise time to first onset of angina as compared to placebo.
- In addition, to prolonging the ETT, and time to first onset of angina, nitroglycerin lingual spray demonstrated statistically significant increases in time to 1 mm ST segment depression for the 0.4, and 0.8 mg nitroglycerin doses when compared to placebo spray ($p\leq 0.0003$; log rank test) during the dosing period suggesting that the anti-anginal effect of the nitroglycerin may be based and anti-ischemic effect.
- Before starting the treadmill exercise, effects on hemodynamic endpoints expected of nitrates, namely, increase heart rate and systolic blood pressure as compared to placebo, were observed.

Of the three doses, used the most appropriate doses that provide clinical benefit are 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate commercial dose. One dose shall be 3 sprays of 0.4 mg each making a total of 1.2 mg.

1.1.6 Safety

Safety

A total of 10 adverse events were reported by 7 (23.3%) patients, all occurring after administration of nitroglycerin spray. Adverse events were reported by 2/30 (6.7%) patients who received 0.2 mg, 1/30 (3.3%) patients who received 0.4 mg and 7/30 (23.3%) who received 0.8 mg of nitroglycerin. All the adverse events were considered to be possibly or probably related to the drug but none of the events were serious or severe. There was no discontinuation. The most common adverse events were headaches (4), fullness in the head (3), hypotension (1) and lightheadedness (2). There were no deaths and no serious adverse events during the study period. There were no changes from baseline in physical examination findings. Treatment with nitroglycerin lingual spray was well tolerated (Tables 20-22). Laboratory measurements were carried out at screening only and therefore no assessment of laboratory changes was performed.

1.1.7 Dosing Regimen and Administration

Nitroglycerin was administered as a lingual spray at dose levels of 0.2, 0.4, 0.8 mg in patients with stable angina appears.

The 0.4 mg dose was significantly better than the 0.2 mg dose.

The 0.8 mg dose is not statistically significantly better than 0.4mg and shows no significant clinical benefit over the 0.4 mg dose.

Of the three doses, used the most appropriate doses that provide clinical benefit are 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate commercial dose. This reviewer agrees with the sponsor.

One dose shall be 3 sprays of 0.4 mg each making a total of 1.2 mg.

1.1.8 Drug-Drug Interactions

Although the half-life of the drug is only 3 minutes and for the recipients about 2 minutes, and the washout period between treatments was 2 hours. There are several drugs that interact with nitroglycerine like other nitrates. See label for nitrates in general. Concomitant use of nitrates and alcohol may cause hypotension. Similarly, the vasodilatory and hemodynamic effects of nitroglycerine may be enhanced by concomitant administration of aspirin.

NovaDel's GTN-S is expected to be similar to other nitrate formulations with other concomitant drugs. Additive hypotensive effects may occur in patients taking GTN concomitantly with anti-hypertensive drugs, beta-adrenergic blockers, phenothiazines, or calcium channel blockers. Oral administration of GTN increases the oral bioavailability of dihydroergotamine, possibly leading to symptomatic ergotism. GTN is contraindicated in patients using cGMP-specific PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil because it potentiates hypotensive effects of organic nitrates. Intravenous GTN decreases the thrombolytic effect of tPA and heparin, therefore patients on these drugs should be closely monitored.

1.1.9 Special Populations

Not applicable.

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2 Introduction and Background

For over one century, nitroglycerin (glycerol trinitrate [GTN]), has been used for the prevention of angina pectoris. Prophylactically, GTN relieves angina pectoris and enhances exertional tolerance. It acts by reducing cardiac oxygen demand through increasing left ventricular pressure and systemic vascular resistance. It also dilates coronary arteries and improves collateral flow to ischemic regions of the heart. The best route of administration for acute relief and lasting effect is through the oral mucosa. The plasma half life of GTN is approximately 1-4 minutes. It is metabolized to active dinitrate metabolites that have a half life of approximately 40 minutes. It is excreted in the urine. Because of its unpredictable course of deterioration when exposed to moisture in the air and its subsequent hydrolysis, the tablets have to be replaced every 3 months. Therefore an aerosol spray formulation that gives longer stability was introduced as a lingual spray in 1985. This was approved by the Agency. Consequent upon the ban of CFC as the propellant in aerosols, a pump spray using air was introduced. It was soon discovered that air had the potential to produce hydrolysis and this led to the substitution of n-butane as the propellant. The FDA was concerned about the safety of butane and this Division has been requested to evaluate both the safety and efficacy of this aerosol nitroglycerin lingual spray as an anti-anginal drug. This is the background to the clinical development program designed by the sponsor.

Product Information

Description of Product: Aerosol Nitroglycerin Lingual spray

Established name and proposed trade name: Aerosol Nitroglycerin lingual spray; Nitroglycerin lingual spray

Chemical class: Organic nitrates.

Pharmacological class: Vasodilator.

Indication:

“Acute relief of an attack and prophylaxis of angina pectoris due to coronary artery disease”.

Dosing regimen

The 0.4 mg dose of the lingual spray was significantly better than the 0.2 mg dose.

The 0.8 mg dose is not statistically significantly better than 0.4mg and shows no significant clinical benefit over the 0.4 mg dose.

Of the three doses, used the most appropriate doses that provide clinical benefit are 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate commercial dose.

One dose shall be 3 sprays of 0.4 mg each making a total of 1.2 mg.

At the onset of an attack one or two metered sprays should be administered into the open mouth. A spray may be repeated approximately every 3 to 5 minutes as needed but no more than 3 sprays are recommended within a 15 minute period. If chest pain persists after a total of 3 sprays

medical attention is indicated. Prior to engaging in activities which might precipitate and attack, a spray may be used prophylactically 5-10 minutes before. During application, the patients should rest in the sitting position and the container held vertically with the spray orifice as close to the mouth as possible. The spray should not be inhaled.

Age groups: Mean age was 66.5 (± 8.8) and the range is 44-81 years old (Table 4).

The sponsor seeks approval for the ~~15 mL~~ (dose size) aerosol bottle of NovaDel's Aerosol Nitroglycerin Lingual spray with the submission of ~~15 mL~~ and ~~stability~~ lots.

The sponsor requests a 3 year patent exclusivity predicated on the requirement to conduct clinical investigations other than bioavailability and/or bioequivalence.

The sponsor has submitted data from independent clinical studies carried out by NovaDel Pharma Inc.

Currently Available Treatment for Indications

The currently available drugs for treatment of acute attack of angina include the following: Sublingual tablets of Nitroglycerin, Nitrostat, Nitroglycerin Capsules, Nitroglycerin Patches, Ointments and intravenous nitroglycerine solution.

Sprays: CFC based nitroglycerine sprays

Availability of Proposed Active Ingredient in the United States

The active ingredients are available in the United States.

Important Issues with Pharmacologically Related Products

Nil

Pre-submission Regulatory Activity

The sponsor was advised to carry out a clinical trial in order to use its own data to support claim for efficacy. The sponsor was advised not to use other data from other drug companies as these were intellectual properties of the company. The minutes of meeting with the sponsor that includes advice and agreements are attached as Appendix 1.

Other Relevant Background Information

All sprays with CFC used as propellant have been banned for environmental reasons.

3 Significant Findings from Other Review Disciplines

Non-clinical data- Biopharm
Not applicable

Pharmacology
Not applicable

Chemistry
Not applicable

CMC (and Product Microbiology, if Applicable)

The drug is manufactured in bulk. Has a DMF for the production of _____ (DMF _____) that is being referenced in this NDA submission. It is designed as a metered aerosol spray 0.4 mg GTN per actuation. GTN and 3 inactive ingredients; caprilic/capric diglycerol succinate, peppermint oil and L (-)-menthol.

Animal Pharmacology/Toxicology

Not applicable

4 Data Sources, Review Strategy, and Data Integrity

The approach used in the delineation of the safety profile of this lingual spray is based on the data supplied by the sponsor from one study and published data (Table 1). In addition the safety update supplied by the sponsor was also reviewed and incorporated in this review.

Sources of Clinical Data

Sources of data are from the following:

Statistical Review of Clinical data

Sponsor's submissions on hard copies of NDA 21780 dated June 16, 2004 volumes 1, 10- 15.

Publications submitted with NDA.

Case report Forms (crf)

IND 64596 Amendment #2

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Tables of Clinical Studies

Table 1: List of Controlled studies and other supportive studies for angina-NDA-21,780

Studies	No/Type of Patients	Design	Treatments and doses	Reference/Location
Controlled clinical studies				
*NovaDel Study FPC 99-033	30 Angina 29 males and 1 female Age range 44-81 years Mean 66.5 yrs	Placebo-controlled, randomized, double-blind, crossover, single center study using butane as a propellant in subjects with chronic stable angina pectoris	GTN-S 0.2, 0.4, and 0.8 mg /spray per activation and placebo	Clinical Study report in NDA Section 8.4.2 Volume 11 page 2
<i>Parker et al., Study</i>	20 Angina	Placebo-controlled, randomized, partially-blind, crossover, single center	GTN-S 0.2, 0.4, and 0.8 mg /spray, placebo Spray, and GTN-SL 0.4 mg	Amer J Cardiol 1986 57 1-5
<i>Kimchi et al., Study</i>	20 Angina	Placebo-controlled, randomized, single-blind, crossover	GTN-S 0.4mg/spray, (Total dose: 0.8 mg) and placebo	Circulation 1983 67 124-127
Other efficacy supportive published studies				
<i>Wight et al.,</i>	783 Angina	Open label	GTN -S 0.4 GTN -S 0.5	Eur J Clin Pharmacol 1992 42 341-342
<i>Kiraly et al.,</i>	82 Angina or other CV disease	Open label	GTN -S 0.4 GTN -S 0.8	Amer J Ther 1998 5 135 - 138
<i>Sato et al.,</i>	17 Angina	Open label Randomized	GTN -S 0.4 GTN -S 0.3	Arzneimittelforschung 1997 47 128-131
<i>Laslett and Baker</i>	50 50 CAD or other CV disease O	Open label randomized	GTN -S 0.4 GTN -S 0.4	Cardiol 1990 77 303 - 310
<i>Shotan et al.,</i>	205	Open label,	GTN -S 0.4	Cardiol 1998 89 163 -

Studies	No/Type of Patients	Design	Treatments and doses	Reference/Location
	<i>Angina</i>	<i>randomized</i>	<i>GTN –S 0.4</i>	169
<i>Ganser et al.,</i>	20 <i>Angina</i>	<i>Double blind randomized</i>	<i>GTN –S 0.4</i> <i>GTN –S 0.4</i>	Cardiovasc Drugs Ther 1990 4 475 – 480
<i>Udvardi</i>	116 <i>Angina</i>	<i>Open label</i>	<i>GTN –S 0.4</i> <i>GTN –S 0.5</i>	Ther Hung 1994 42 45 – 47
<i>Kethelyi</i>	173 <i>Angina</i>	<i>Open label</i>	<i>GTN –S 0.4</i> <i>GTN –S 0.5</i>	Ther Hung 1992 40 173-176

CAD=Coronary Artery Disease; CV=Cardiovascular; GTN=nitroglycerin; ISDN=isosorbide dinitrate; S=Spray; SL= Sublingual tablet

Review Strategy

The sponsor's volumes, in hard copies, were the main sources of data and information for this review. The volumes that provided the most clinical information were 1, and 10 -15. Copies of reprints from the supportive studies were also used as sources of reference and to support safety and efficacy. The only trial submitted by the sponsor was reviewed for efficacy. This reviewer was the sole reviewer for the clinical section of this NDA. Consultations with other reviewers dealing with Chemistry, pharmacology and biopharm were carried out including internal meetings.

Data Quality and Integrity

Not applicable. No audit required.

Compliance with Good Clinical Practices

The study was carried out using good clinical practice.

Financial Disclosures

In compliance with regulations, the sponsor and the investigators have certified that there are no financial arrangements between them that could have affected the outcome of these studies and that the data from these studies have not been affected by any form of compensation. The approved form, OMB No 0910-0396, was signed by the President and CEO, Gary A. Shangold, on 7/14/04 for and on behalf of the sponsor.

5 Clinical Pharmacology

Not applicable because there are similar approved products.

Pharmacokinetics

A pilot PK study of the spray at 0.4 mg per activation under fasting conditions (study FPC 99-003) demonstrated that NovaDel GTN-S produced blood levels of GTN, 1,2-GDN and 1,3-GDN in all subjects in the study and that the PK parameters for all three were within the historic range found for other lingual sprays and oral formulations reported in the literature. Nitroglycerin is rapidly absorbed following lingual spray administration. In the PK study when a single 1.2 mg dose was administered to 12 healthy volunteers the T_{max} was 8.25 minutes and the C_{max} values had a coefficient of variation (CV) in the range of 80-100%. The volume of distribution following I.V. administration was 3.3 L/kg and plasma concentrations between 50 and 500 ng/ml, binding to plasma proteins was approximately 60%, while that of 1,2 dinitroglycerin and 1,3 dinitroglycerin was 60% and 35 % respectively.

A liver reductase enzyme is of primary importance in the metabolism of GTN. Known sites of extrahepatic metabolism include red blood cells and vascular walls. Mean elimination half life of metabolites is 40 minutes

Pharmacodynamics

This is a well known drug belonging to the class of nitrates. See Tables 6-9, 13 and 17 for PD effects.

Exposure-Response Relationships

Not applicable because this is a well known drug belonging to the class of nitrates. Exposure to drug is in Table 19. Response to drug exposure is graphically represented in Figures 1-4. Note treatment effect of 0.4mg in this crossover study (N=30). No significant outliers to explain data in Figure 2.

Figure 2: Scattergram of individual efficacy response data (N=30). 4 sequence period crossover - time from exercise start to onset of angina. Source- Reviewer - FPC 99-003

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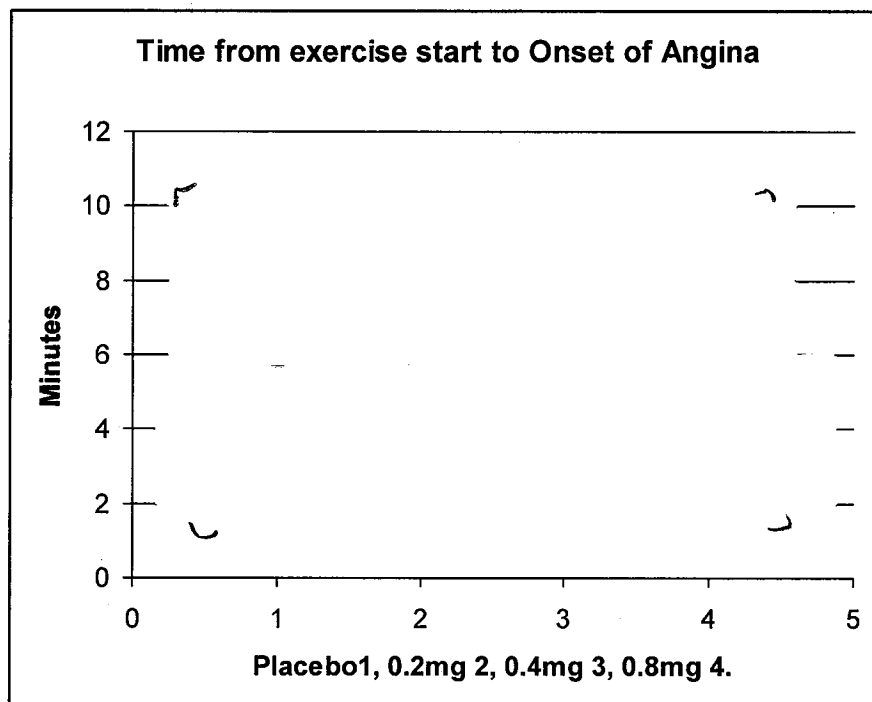


Table 2: Statistical Analysis of exercise time to onset of angina (N=30) - FPC-99-003

Treatment	William's Mean Estimate	P-value comparing dose to placebo
Placebo	5.30	---
0.2mg	5.84	0.0001
0.4mg	6.14	<0.0001
0.8mg	6.29	<0.0001

Table 3: Reasons to stop exercise among treatment groups - FPC 99 -003

Parameter	Placebo	0.20 mg	0.40 mg	0.80 mg
Angina	30/30 (100%)	26/30 (86.7%)	25/30 (83.3%)	24/30 (80%)
Other reasons	0/30	4/30 (13.3%)	5/30 (16.7%)	6/30 (20%)
Pvalue(1)		0.1124	0.0522	0.0237
Pvalue(2)		0.7306	1.00	
Pvalue(3)		1.000		

Pvalue (1) Nitroglycerin vs placebo

Pvalue (2) 0.8mg nitroglycerin vs 0.2 and 0.4 mg nitroglycerin

Pvalue (3) 0.2mg vs 0.4 mg nitroglycerin treatment group

Integrated Review of Efficacy

The primary efficacy analysis included comparing 1) each of the four treatments with no treatment at screening (baseline) for change in ETT to onset of moderate angina and 2) each of

the 3 GTN treatments with placebo for differences in the magnitude of this ETT change. This approach was used to evaluate treatment differences for changes in secondary efficacy parameters. Thirty patients were enrolled in the study and they all completed the study and were included in the efficacy analysis.

There is one small study of 30 subjects in a 4 way crossover design - Novadel study FPC99-003. Since there is only one efficacy study there is no need for an integrated study of efficacy.

The demographic and baseline characteristics for all the 30 randomized subjects are in Table 4 below.

Table 4: – Demographics - FPC 99-033

Characteristics	Total N=30
Age (yrs). n (%)	
<21	0
21-44	1(3.3)
45-64	11(36.7)
>65	18(60.0)
Mean (SD)	66.5(8.8)
Range	44-81
Gender	
Male	29(96.7)
Female	1(3.3)
Race	
Caucasian	30(100)
Weight (kg)	
Mean (SD)	86.8(13.0)
Range	68-135
Height (cm)	
Mean	173.2(6.6)
Range	152-182

SD= Standard Deviation; Range = Minimum - maximum

The primary efficacy measurements for the different treatment groups are in Table 5 below. Compared with placebo all three doses of GTN showed statistically significant increase in the change in exercise treadmill time (ETT) ($p < 0.0003$). This reflects the overall treatment effect. There was a dose response relationship for prolonging the mean time to development of moderate angina (Figures 3 and 4). Statistically significantly greater effects were seen when either the 0.4 or 0.8 mg GTN-S dose was compared with 0.2 mg dose ($p = 0.0095$ and $p = 0.0004$, respectively). The 0.4 mg and 0.8 mg doses showed no statistically significant difference when compared to each other (Table 5).

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Table 5: Changes in ETT to development of moderate angina - Study FPC 99 -003

Parameter	Placebo	0.2mg	0.4mg	0.8mg
N	30	30	30	30
Mean (SD) at Baseline	4.60	4.60	4.60	4.60
Mean (SD) at endpoint	5.30	5.81	6.16	6.30
LS Mean Change (SE)	0.69	1.20	1.56	1.70
Percent change relative to Placebo LS Mean Change		+73.9	+126.1	+146.4
p-value ^a	0.0001	-	-	-
p-value ^b	-	0.0003	0.0001	0.0001
p-value ^c	-	0.0004	0.3036	-
p-value ^d	-	0.0095	-	-

p-value^a for the overall treatment effect.

p-value^b for comparisons of nitroglycerin treatment groups versus placebo.

p-value^c for comparisons of 0.8 mg nitroglycerin treatment group vs. 0.2 and 0.4 mg nitroglycerin treatment

p-value^d comparison of 0.2 mg nitroglycerin treatment group vs. 0.4 mg nitroglycerin treatment group.

Table 6: Mean changes in exercise time (minutes) to development of moderate angina

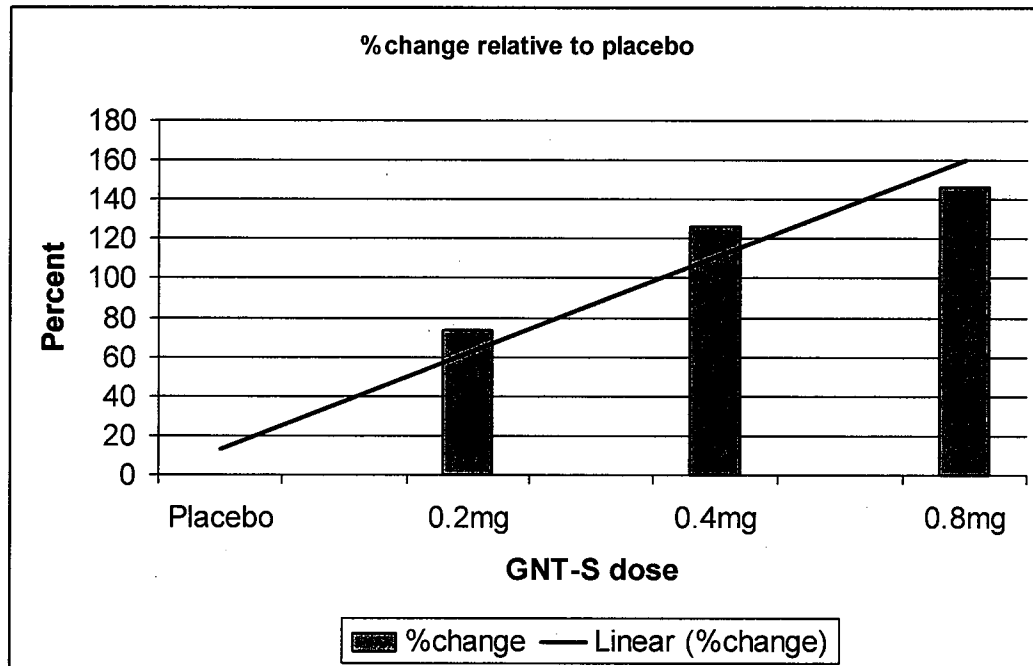
Exercise time (minutes)	Placebo	0.2mg	0.4mg	0.8mg
Mean $\pm$ Std Dev	5.30 $\pm$ 1.50	5.84 $\pm$ 1.67	6.14 $\pm$ 1.08	6.29 $\pm$ 1.89
Range	3.05 – 8.55	3.55 – 9.18	3.85 – 9.87	3.43 – 9.35
P value (comparing dose to placebo)	---	0.0001	<0.0001	<0.0001

Concomitant Medication

A review of concomitant medications reported to have been taken by subjects during the double-blind phase of study showed no changes compared with those reported taken at screening.

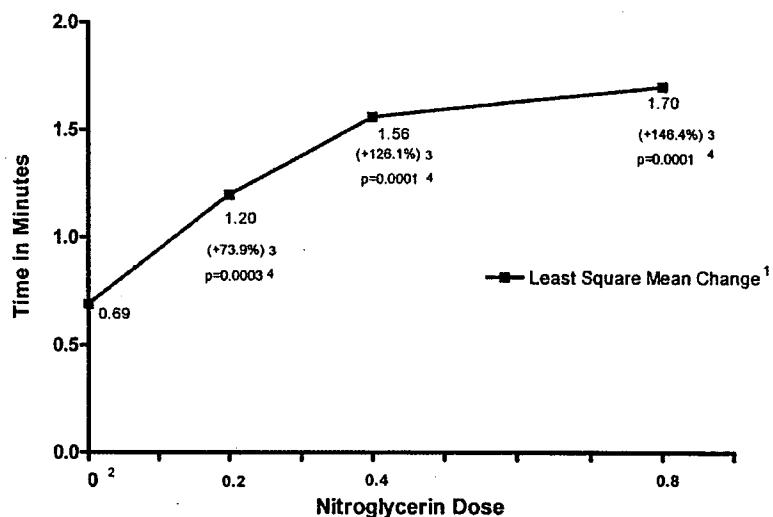
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Figure 3: Percent change in Exercise Treadmill Times (minutes) ETT relative to placebo -FPC 99-003-Source Reviewer. Shows more than 20% change over placebo for each of the dose levels.



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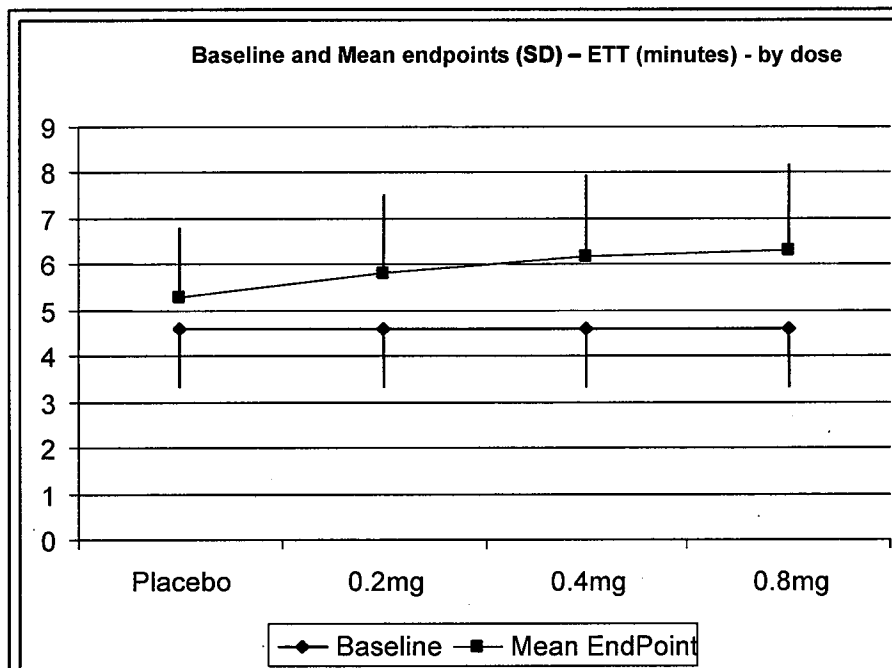
Figure 4: Mean Changes (SD) in ETT from baseline to end point by dose - FPC 99 -033-Source-Reviewer



- 1 Least square mean change for the difference: Investigational Drug ETT – Control (Screening) ETT.
- 2 0 mg represents placebo treatment group.
- 3 Percent change relative to placebo least square mean change.
- 4 P-value for the comparisons of nitroglycerin treatment groups versus placebo.

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Figure 5: Baseline and Endpoints (SD) by dose-FPC99-003-Source - Reviewer



Tables 7- 11, 13 -17 and graphs in Figures 6-9 support the secondary efficacy conclusions on page 11 of the executive summary and in this review.

Table 7: Time to change in Heart rate (minutes) FPC 99-003

Time to change in HR	Placebo	0.2mg	0.4mg	0.8mg
Mean ± Std Dev	2.76 ± 0.81	3.56 ± 1.45	3.38 ± 1.32	3.91 ± 1.29
Range	1.67-6.00	1.55-6.00	1.63-6.00	2.83-6.00
P value (comparing dose to placebo)		0.0196	0.0223	0.0006

Table 8: Time (minutes) to change in Systolic Blood Pressure - FPC99-033

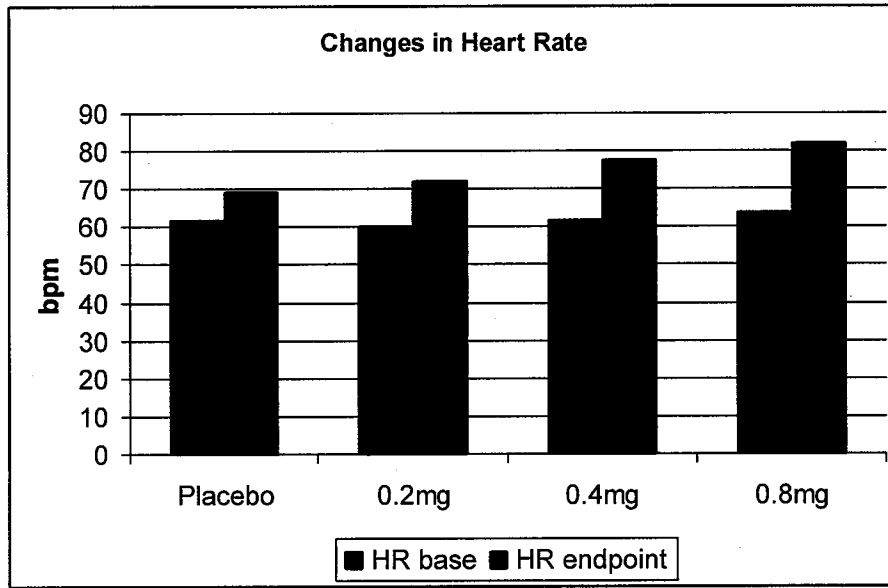
Time to change in SBP	Placebo	0.2mg	0.4mg	0.8mg
Mean ± Std Dev	3.13 ± 1.47	3.05 ± 0.86	2.93 ± 0.65	3.03 ± 0.24
Range	1.67-8.83	1.55-6.00	1.63-5.08	2.83-4.30
P value (comparing dose to placebo)	--	0.6465	0.7342	0.7683

Table 9: Time (minutes) to develop 1 mm ST segment depression on ECG-FPC99-003

Time to change in 1mm ST depression	Placebo	0.2mg	0.4mg	0.8mg
Mean ± Std Dev	4.69 ± 1.58	6.05 ± 1.68	5.65 ± 2.03	5.99 ± 2.13
Range	2.05 – 7.25	3.58 – 9.18	2.83 – 9.30	2.88 -9.13
P value (comparing dose to placebo)	--	0.0003	0.0006	0.0005

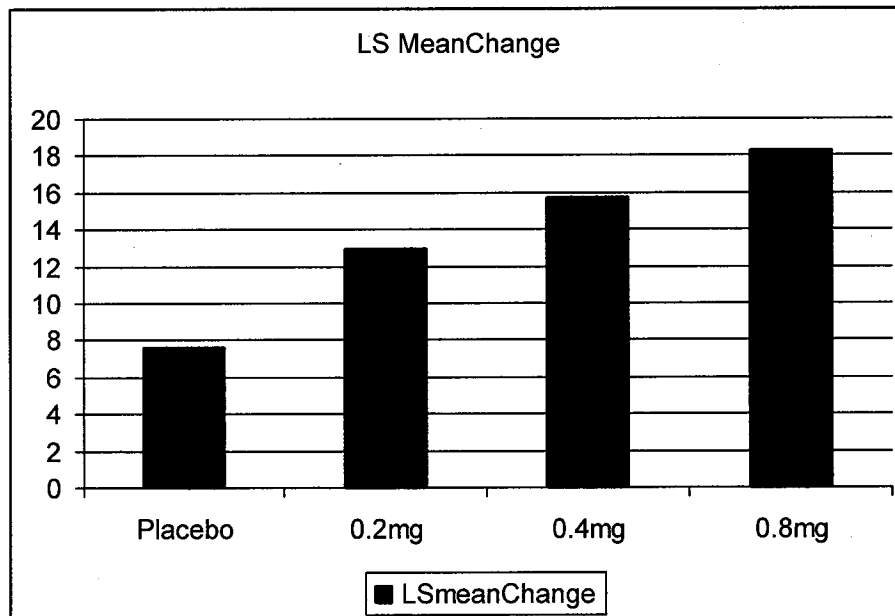
Heart Rate

Figure 6: Changes in Heart rate from baseline to endpoint - Source - Reviewer



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Figure 7: Mean Change in heart rate from baseline to endpoint- Source- Reviewer



Systolic Blood Pressure

Figure 8: Change in Systolic Blood Pressure from baseline to endpoint-Source- Reviewer

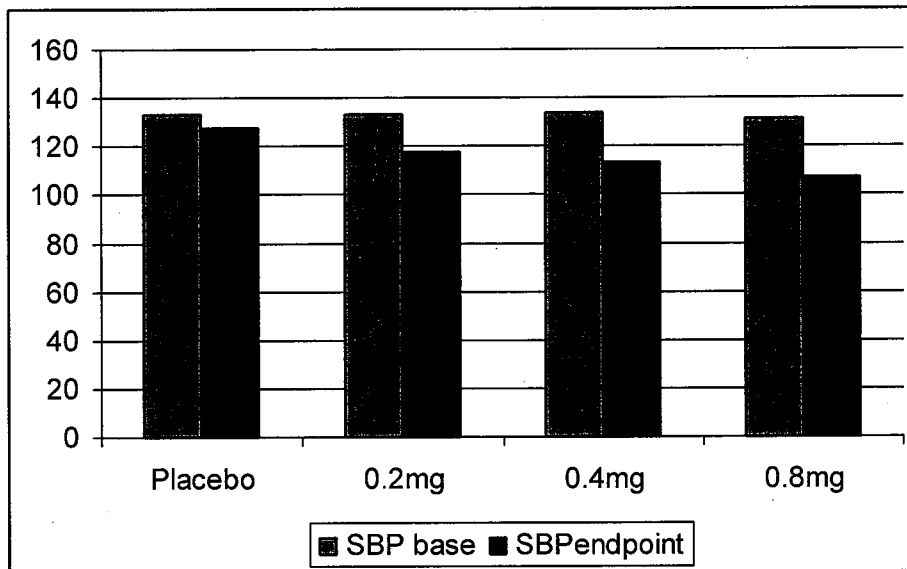
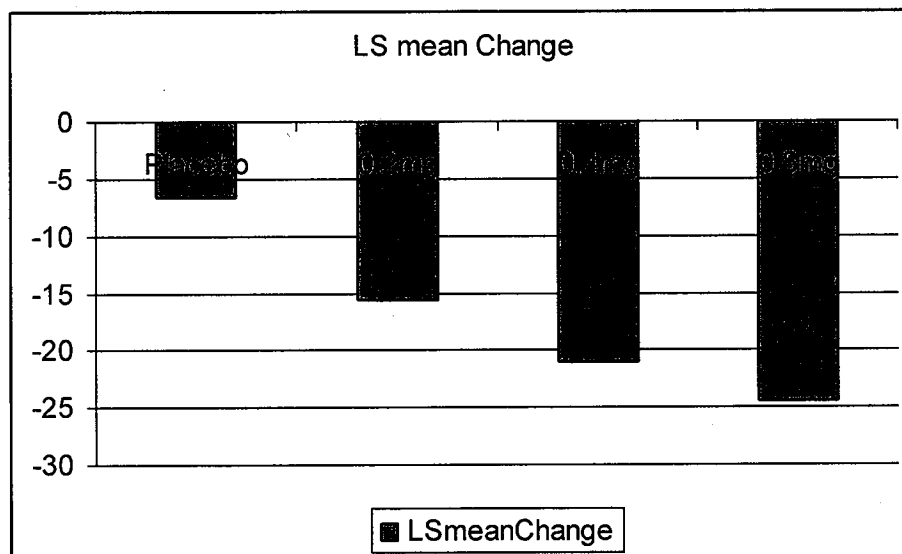


Figure 9: Mean changes in systolic blood pressure by dose-Source- Reviewer-FPC-99-003



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Comparison of clinical findings between Novadel GTN-S-sponsored study with counterpart findings from published studies of other GTN formulations showed similarities in efficacy and safety profiles (Tables 1, 10 and 11).

Table 10: Comparative evaluation of changes in ETT from control to development of Moderate angina and to first onset of angina- Novadel FPC-99-003

	Placebo		0.2-mg spray		0.4-mg spray		0.8-mg spray		0.4-mg GTN sublingual Tablet	
	ETT ^M	ETT ^F	ETT ^M	ETT ^F	ETT ^M	ETT ^F	ETT ^M	ETT ^F	ETT ^M	ETT ^F
Novadel Control	276	211	276	203	276	207	276	199	N/A	N/A
Endpoint	318	245	349	262	370	285	378	280		
Change ^a	+42	+34	+73	+59	+94	+78	+102	+81		
Parker Control ^b	362	281	355	283	355	284	362	290	371	289
Endpoint	383	308	459	401	489	428	505	457	529	463
Change	+21	+27	+109	+118	+134	+144	+143	+167	+158	+174
Kimchi Control	300	N/A	N/A	N/A	N/A	N/A	321	N/A	N/A	N/A
Endpoint	312	N/A					420	N/A		
Change	+12 ^a	+17					+99 ^a	+100		

^a Change = mean Endpoint value – mean control value M=Time to devpt.of moderate angina

^b Control = mean Endpoint value – mean change value. F=Time to first onset of angina

Table 11: Comparative evaluation of changes in Heart rate from the last pre-exercise measurement to development of Moderate Angina and to first onset of angina

	Placebo		0.2-mg spray		0.4-mg spray		0.8-mg spray		0.4-mg GTN sublingual Tablet	
	HR ^M	HR ^F	HR ^M	HR ^F	HR ^M	HR ^F	HR ^M	HR ^F	HR ^M	HR
Novadel Control	69.23	69.23	72.23	73.50	77.67	76.30	82.13	80.92	N/A	N/A
Endpoint	114.80	106.90	119.27	110.73	122.30	112.19	124.70	114.56		
Change	+45.50	+37.67	+46.00	+37.14	+44.55	+35.91	+42.44	+33.58		
Parker Control	72	72	78	78	83	83	84	84	81	81
Endpoint	116	109	121	116	122	122	129	125	125	121
Change	+44	+37	+43	+38	+39	+39	+45	+41	+44	+40
Kimchi Control	118	N/A	N/A	N/A	N/A	N/A	122	N/A	N/A	N/A
Endpoint	120						137			
Change	+2						+15			

Indication

“Acute relief of an attack and prophylaxis of angina pectoris due to coronary artery disease”. This reviewer is of the opinion that the indication should be “~~Acute relief of an attack and prophylaxis of angina pectoris due to coronary artery disease~~”. The latter suggestion places emphasis on “~~Acute relief of an attack and prophylaxis of angina pectoris due to coronary artery disease~~”. Furthermore, nitrates are used for the treatment and prevention of attacks of angina.

5.1.1 Methods

The clinical data used for this review are to a very large extent from the results of NoveDel’s sponsored study FC 99-033, and to a very small extent from NovaDel’s sponsored PK study -131-63-11700.

Protocol: Study design

Screening: Screening of patients used the Bruce protocol. Subjects who developed angina between 2 and 9 minutes on a treadmill exercise test were eligible to participate in the study. Sixty minutes after the first exercise test, 0.4 mg of nitroglycerin lingual spray was administered and a second exercise test was conducted 5 minutes later. Patients who improved on their exercise time by 20 percent or by 60 seconds were considered to be nitrate responders and were eligible to continue in the study. Subjects must have shown reproducible exercise times as defined in the protocol.

Double blind phase of the study: Thirty patients were randomly assigned to 1 of 4 treatment sequences. Each treatment sequence consisted of 4 treatment periods in a prespecified order. Exercise tests were conducted on 2 study days (2 treatments/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.

Efficacy was the exercise treadmill time (ETT) to the development of moderate angina following the administration of 3 sprays of aerosol (0.2, 0.4, 0.8 mg per activation) and placebo lingual spray. Safety evaluation included the collection of adverse events and discontinuation/completion data. Efficacy summaries were based on the I-T-T population defined as the population of randomized patients who received at least 1 dose of the double-blind treatment and had at least 1 post-randomization measurement of efficacy obtained.

The primary measure of efficacy was change in ETT (investigational ETT – control [screening] ETT) to the development of moderate angina following the double blind administration of 3 sprays of aerosol nitroglycerin spray (0.2, 0.4, 0.8 mg) and placebo lingual spray. An analysis of variance (ANOVA) was performed to detect between-different differences in the changes from screening to the double-blind treatment in the primary efficacy variable (ETT).

5.1.2 General Discussion of Endpoints

5.1.3 Study Design

- This is a well designed study that evaluated the effectiveness of the nitroglycerine spray that has butane as the propellant. The study was randomized and double blinded and well controlled. The dose finding was adequate and satisfactory.

5.1.4 Efficacy Findings

The results of the only clinical trial support efficacy for the proposed indication.

The primary efficacy measurements for the different treatment groups are in Table 5. Compared with placebo all three doses of GTN showed statistically significant increase in the change in exercise treadmill time (ETT) ($p < 0.0003$). This reflects the overall treatment effect. There was a dose response relationship for prolonging the mean time to development of moderate angina (Figure 1). Statistically significantly greater effects were seen when either the 0.4 or 0.8 mg GTN-S dose was compared with 0.2 mg dose ($p = 0.0095$ and $p = 0.0004$, respectively). The 0.4 mg and 0.8 mg doses showed no statistically significant difference when compared to each other (Table 5).

Table 12: Changes in ETT (minutes) - FPC – 99-003

Parameter	Placebo	0.2mg	0.4mg	0.8mg
N	30	30	30	30
Mean (SD) at Baseline	4.60	4.60	4.60	4.60
Mean (SD) at endpoint	5.30	5.81	6.16	6.30
LS Mean Change (SE)	0.69	1.20	1.56	1.70
Percent change Relative to Placebo LS Mean Change		+73.9	+126.1	+146.4
P value ^a	0.0001	-	-	-
P value ^b	-	0.0003	0.0001	0.0001
P value ^c	-	0.0004	0.3036	-
P value ^d	-	0.0095	-	-

p-value^a for the overall treatment effect.

p-value^b for comparisons of nitroglycerin treatment groups versus placebo.

p-value^c for comparisons of 0.8 mg nitroglycerin treatment group vs. 0.2 and 0.4 mg nitroglycerin treatment

p-value^d comparison of 0.2 mg nitroglycerin treatment group vs. 0.4 mg nitroglycerin treatment group.

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Figure 10: Percent change of ETT by dose relative to placebo FPC99-003 -Source - Reviewer

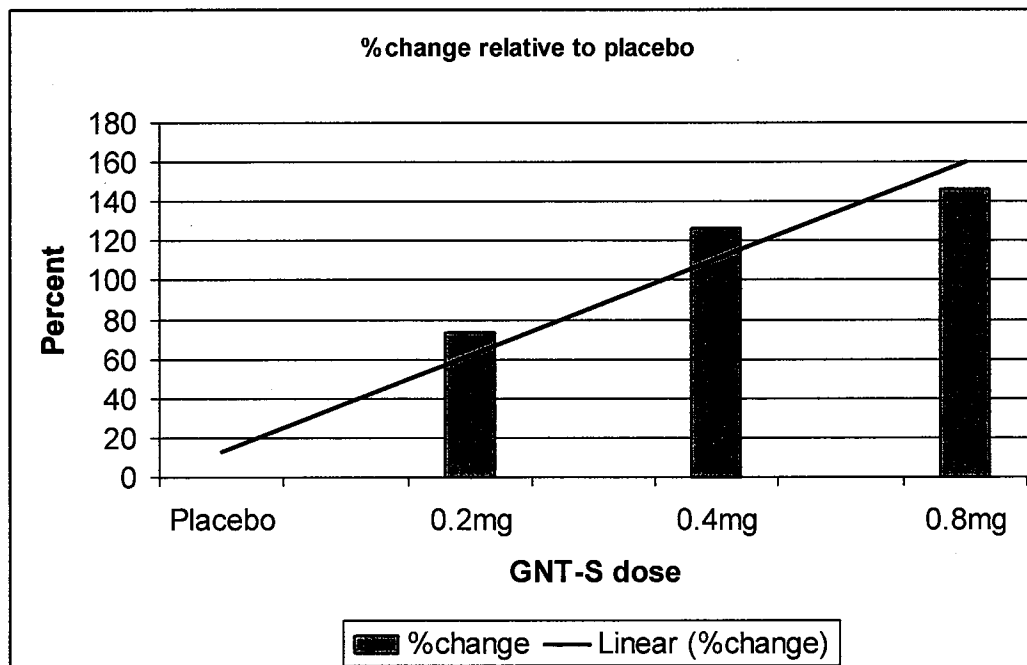


Table 13: Changes in ETT to the first onset of angina from baseline to endpoint-FPC 99-003

	Placebo	0.2mg GTN	0.4mg GTN	0.8mg GTN
N	30	26	27	25
Mean (SD) at baseline	3.52(1.49)	3.39(1.48)	3.45(1.40)	3.32(1.47)
Mean (SD) at baseline	4.09(1.52)	4.36(1.79)	4.75(1.91)	4.67(2.08)
Least Square Mean Change (SE)	0.57(0.13)	0.88(0.15)	1.30(0.14)	1.26(0.15)
P-value ^a	0.0007	-	0.0003	-
P-value ^b		0.1081	0.8180	0.0008
P-value ^c		0.678	-	-
P-value ^d		0.0364	-	-

p-value^a for the overall treatment effect.

p-value^b for comparisons of nitroglycerin treatment groups versus placebo.

p-value^c for comparisons of 0.8 mg nitroglycerin treatment group vs. 0.2 and 0.4 mg nitroglycerin treatment

p-value^d comparison of 0.2 mg nitroglycerin treatment group vs. 0.4 mg nitroglycerin treatment group.

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Table 14: Time to development of 1 mm ST segment depression (minutes) for all subjects-FPC 99-033

	Placebo	0.2mg GTN	0.4mg GTN	0.8mg GTN
N ^a	30	30	30	30
Median time	5.83	8.08	9.30	9.13
P-value ^b	-	0.0912	0.0467	0.0045
P-value ^c	-	0.1911	0.6685	-
P-value ^d	-	0.3518	-	-

^a for all treated subjects.

p-value^b for comparisons of nitroglycerin treatment groups versus placebo.

p-value^c for comparisons of 0.8 mg nitroglycerin treatment group vs. 0.2 and 0.4 mg nitroglycerin treatment

p-value^d comparison of 0.2 mg nitroglycerin treatment group vs. 0.4 mg nitroglycerin treatment group.

Table 15: Time to development of 1 mm ST segment depression (minutes) in subjects with events during any dosing period –PK study 131-63-11700

	Placebo	0.2mg GTN	0.4mg GTN	0.8mg GTN
N	12	10	8	7
LS mean (SE)	4.59(0.19)	6.11 (0.21)	6.00 (0.25)	6.39 (0.27)
P-value ^b	0.0001	-	-	-
P-value ^c	-	0.0001	0.0003	0.0001
P-value ^d	-	0.4030	0.3051	-
p-value ^e	-	0.7565	-	-

Table 16: Time to development of 1 mm ST segment depression (minutes) in subjects with event during placebo period - PK study 131-63-11700

	Placebo	0.2mg GTN	0.4mg GTN	0.8mg GTN
N ^f	12	12	12	12
LS mean (SE)	4.59 (0.17)	6.06 (0.17)	6.02(0.17)	6.36(0.17)
P-value ^b	0.0001	-	-	-
P-value ^c	-	0.0001	0.0001	0.0001
P-value ^d	-	0.2277	0.1693	-
p-value ^e	-	0.8575	-	-

p-value^a for the number of patients who developed 1 mm ST segment depression during any dosing period.

p-value^b for the overall treatment effect

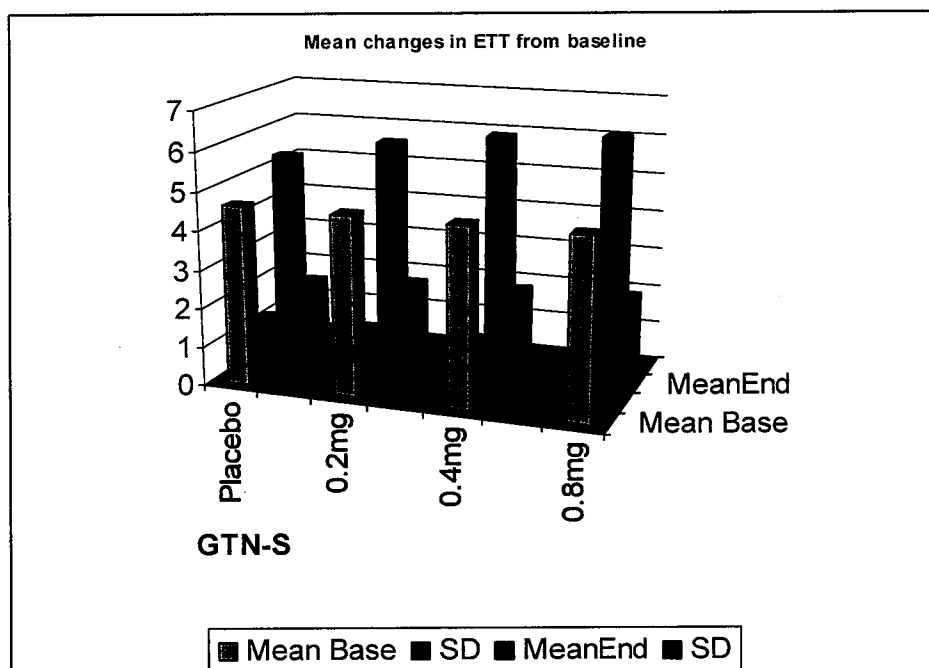
p-value^c for comparisons of nitroglycerin treatment groups versus placebo.

p-value^d for comparisons of 0.8 mg nitroglycerin treatment group vs. 0.2 and 0.4 mg nitroglycerin treatment

p-value^e comparison of 0.2 mg nitroglycerin treatment group vs. 0.4 mg nitroglycerin treatment group.

^fhe number of subjects who developed 1 mm ST segment depression during placebo period.

Figure 11: Mean changes in ETT (minutes) from baseline by dose-Source – Reviewer (see Figure 3)



GTN = Nitroglycerine

Table 17: Secondary efficacy evaluation - FPC 99-033

Parameters	Placebo	0.2 mg GTN-S	0.4 mg GTN-S	0.8mg GTN-S
Mean Change in ETT to the first onset of angina from baseline to endpoint (mins)	0.57 (0.13)	0.88 (0.15)	1.30 (0.14)*	1.26 (0.15)
Mean Change in Standing HR from before dosing to after dosing (bpm)	7.64 (0.75)	12.99 (0.75)*	15.73 (0.75)*	18.31 (0.75)*
Mean Change in Standing SBP from before dosing to after dosing (mmHg)	-6.16 (1.73)	-15.58 (1.73)*	-20.96 (1.73)*	-24.14 (1.73)*
Mean Change in Standing DBP from before dosing to after dosing (mmHg)	0.24 (0.77)	-1.28 (0.79)	-2.08 (0.77)*	-1.91 (0.77)
Mean Change in Standing RPP from before dosing to after dosing ()	6.01 (1.47)	5.97 (1.47)	4.83 (1.47)	4.16 (1.47)
Mean Change in Standing HR from after dosing to moderate angina (bpm)	45.50 (1.05)	46.00 (1.05)	44.55 (1.05)	42.44 (1.05)*
Mean Change in Standing SBP from after dosing to moderate angina (mmHg)	34.72 (2.09)	49.29 (2.09)*	56.13 (12.09)*	60.62 (2.09)*
Mean Change in Standing DBP from after dosing to moderate angina (mmHg)	4.37 (0.88)	5.49 (0.90)	6.65 (0.88)	6.87 (0.88)*
Mean Change in Standing RPP from after dosing to moderate angina (mmHg)	98.83 (3.24)	113.80 (3.24)*	120.25 (3.24)*	122.54 (3.24)*
Mean Change in Standing HR from after	37.67	37.14	35.91	33.58

Parameters	Placebo	0.2 mg GTN-S	0.4 mg GTN-S	0.8mg GTN-S
dosing to first onset of angina (mmHg)	(1.14)	(1.29)	(1.25)	(1.32)*
Mean Change in Standing SBP from after dosing to first onset of angina (mmHg)	30.49 (2.42)	42.26 (2.76)*	48.44 (2.67)*	55.58 (2.81)*
Mean Change in Standing DBP from after dosing to first onset of angina (mmHg)	1.94 (1.19)	4.34 (1.39)	5.88 (1.31)	5.74 (1.38)*
Mean Change in Standing RPP from after dosing to first onset of angina (mmHg)	81.46 (3.75)	91.25 (4.26)	97.46 (4.13)*	101.75 (4.35)*
Median time to development of 1-mm ST segment depression (minutes).	5.83	8.08	9.30*	9.13*

* GTN dose is statistically significantly different from placebo ($p < 0.05$). ** ***

5.1.5 Clinical Microbiology

Not applicable.

5.1.6 Efficacy Conclusions

Efficacy

An overall treatment effect on the time to development of moderate angina was highly significant ($p = 0.0001$). Compared with placebo, all 3 nitroglycerin dose levels showed significantly prolonged ETT to development of moderate angina ($p \leq 0.0003$). A clear dose response relationship was also observed for prolonging the time to development of moderate angina. Both the 0.4 mg and 0.8 mg dose levels were significantly better in prolonging ETT when compared with the 0.2 mg dose level ($p = 0.0095$ and $p = 0.0004$, respectively). However there was no statistically significant difference between the 0.4 and 0.8 mg dose levels ($p = 0.3036$).

Conclusions:

- Nitroglycerin lingual spray (0.2, 0.4, 0.8 mg per activation) resulted in increase in exercise time to first onset of angina as compared to placebo.
- In addition, to prolonging the ETT, and time to first onset of angina, nitroglycerin lingual spray demonstrated statistically significant increases in time to 1 mm ST segment depression for the 0.4, and 0.8 mg nitroglycerin doses when compared to placebo spray ($p \leq 0.0003$; log rank test) during the dosing period suggesting that the anti-anginal effect of the nitroglycerin may be based and anti-ischemic effect.
- Before starting the treadmill exercise, effects on hemodynamic endpoints expected of nitrates, namely, increase heart rate and systolic blood pressure as compared to placebo, were observed.

6 Integrated Review of Safety

There is only one study so there is no integrated review of safety. However, the numbers of patients reporting adverse events in NovaDel studies, FPC99-003 and PK study 131-63-11700, and published placebo-controlled studies are presented in Tables 18 -20 below. Table 22 summarizes the frequencies of adverse events in the clinical study FPC99-003.

Table 18: Number (%) of patients with AEs in Novadel and placebo-controlled published studies-FPC99-003

Novadel Studies							Published studies			
AE	Study FPC 99-003 Cross-over study					PK study	Parker et al 1986		Kimchi et al., 1983	
	*Pl cbo	GTNS 0.2 mg	GTNS 0.4 mg	GTNS 0.8 mg	Overall GTNS		Plcbo	0.2,0.4, 0.8 & 0.4mg GTNS-L	Plcbo	GTNS 0.8 mg
Total N	30	30	30	30	30	12	20	20	20	20
Any Adverse Ev.	0	2(7)	1(3)	7(23)	7(23)	9(75)	-	4(25)	-	3(15)
Nervous system d										
Headache NOS	0	1(3)	1(3)	5(17)	5(17)	5(42)				
Somnolence	0	0	0	0	0	3(36)				
Dizziness	0	1(3)	0	1(3)	1(3)	1(8)				
Vascular disorders							-		-	
Hypotension NOS	0	0	0	1(3)	1(3)	0		0		0
Cardiac disorders							-		-	
Palpitations	0	0	0	0	0	1(8)		0		0
Eye disorders							-		-	
Vision abnormal	0	0	0	0	0	1(8)		0		0
Psychiatric dis.							-		-	
Disorientation	0	0	0	0	0	1(8)		0		0
Endocrine dis.							-		-	
Low glucose	0	0	0	0	0	1(8)		0		0
Investigations							-		-	
Neutrophils ↓	0	0	0	0	0	1(8)		0		0
Urinalysis abnormal	0	0	0	0	0	1(8)		0		0
Skin and Subcut.							-		-	
Skin Irritation	0	0	0	0	0	1(8)		0		0

- *Adverse events were not provided for placebo treatment.
- AEs were not provided by treatment groups.

Drug exposure and Extent of exposure

There were no blood levels taken in this clinical study FPC99-033. All 30 subjects received 5 separate administrations of nitroglycerin: 0.4 mg during the screening phase 60 minutes after the first exercise test to establish their nitrate sensitivity; 0.4 mg 5 minutes prior to the performance of the second exercise test to demonstrate reproducibility; and 0.2, 0.4, 0.8 mg aerosol nitroglycerine spray once each during the double blind treatment phase. All subjects were given placebo spray during the double-blind treatment phase (Table 8).

Table 19: Drug Exposure - FPC 99-003

	*Plcbo	GTNS 0.2 mg	GTNS 0.4 mg	GTNS 0.8 mg	Overall GTNS	GTNS 1.2 mg
Total N	30	30	30	30	30	12

6.1.1 Deaths

There were no deaths.

6.1.2 Other Serious Adverse Events

There were no serious adverse events and no subject dropped out during the study.

Adverse events

Table 20: Percent (%) of patients with adverse events – FPC 99-033

Adverse Event	Placebo	0.2mg	0.4mg	0.8mg	All
Any adverse event	0	2(6.7)	1(3.3)	7(23.3)	7(23.3)
Fullness in head	0	0	0	3(10.0)	3(10.0)
Headache	0	1(3.3)	1(3.3)	2(6.7)	2(6.7)
Lightheadedness	0	1(3.3)	0	1(3.3)	1(3.3)
Hypotension	0	0	0	1(3.3)	1(3.3)

Table 21: Summary of adverse events by body system- PK study-131-63-11700

Body system	Adverse Event	All events (N=12)	Drug related events
Body	Headache	5(42%)	5(42%)
	Pounding in chest	1(8%)	1(8%)
Hematological	Decreased absolute neutrophils	1(8%)	0(0%)
Metabolic/Nutritional	Low glucose	1(8%)	0(0%)
Neurological	Disorientation	1(8%)	1(8%)
	Lightheaded	1(8%)	0(0%)
	Sleepiness	3(25%)	3(25%)
Dermatological	Skin irritation	1(8%)	0(0%)
Special Senses	Visual Red	1(8%)	1(8%)
	White flashes		
Urogenital	Abnormal U/A	1(8%)	0(0%)

Table 22: Adverse events during double-blind treatment phase - FPC 99-003

Patient No	Term	Drug dose	Duration of AE	Intensity	Relationship	SAE
3	Hypotension	0.8mg	1min	Moderate	Probably	No
5	Fullness in the	0.8mg	5 min	Mild	Probably	No

Patient No	Term	Drug dose	Duration of AE	Intensity	Relationship	SAE
	head					
7	Fullness in the head	0.8mg	3 min	Mild	Probably	No
10	Headache	0.8mg	8 min	Mild	Probably	No
20	Lightheadedness	0.2mg	2 min	Mild	Probably	No
	Lightheadedness	0.8mg	2 min	Mild	Probably	No
22	Fullness in the head	0.8mg	4 min	Mild	Possibly	No
26	Headache	0.2mg	8 min	Mild	Probably	No
	Headache	0.4mg	24 min	Moderate	Probably	No
	Headache	0.8mg	9 min	Moderate	Probably	No

6.1.3 Dropouts and Other Significant Adverse Events

There were no discontinuations and no dropouts.

6.1.3.1 Overall profile of dropouts

There were no dropouts.

6.1.3.2 Adverse events associated with dropouts

Not applicable

6.1.3.3 Other significant adverse events

Not applicable

6.1.4 Other Search Strategies

6.1.5 Common Adverse Events

See table 22

6.1.5.1 Eliciting adverse events data in the development program

Not applicable

6.1.5.2 Appropriateness of adverse event categorization and preferred terms

Not applicable

6.1.5.3 Incidence of common adverse events

Not applicable

6.1.5.4 Common adverse event tables

Table 22

6.1.5.5 Identifying common and drug-related adverse events

Table 22

6.1.5.6 Additional analyses and explorations

Not applicable

6.1.6 Less Common Adverse Events

Not applicable

6.1.7 Laboratory Findings

There were no laboratory evaluations after the baseline data. Therefore, there are no data for analysis.

6.1.7.1 Overview of laboratory testing in the development program

There were no laboratory evaluations after the baseline data. Therefore, there are no data for analysis. Not applicable

6.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.7.3 Standard analyses and explorations of laboratory data

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.7.3.1 *Analyses focused on measures of central tendency*

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.7.4 Additional analyses and explorations

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.7.5 Special assessments

There were no laboratory evaluations after the baseline data. Therefore there are no data for analysis.

6.1.8 Vital Signs

Table 17 and Figures 7-9.

6.1.8.1 Overview of vital signs testing in the development program

This was considered adequate as these were in secondary efficacy measures. Blood pressure (sitting) and apical heart rates measurements were obtained prior to study drug administration. In order to avoid orthostatic effects, patients were instructed to be cautious when moving from supine to sitting position to the upright position. Only light activity was permitted during the study day.

6.1.8.2 Selection of studies and analyses for overall drug-control comparisons

There is only one study. Not applicable

6.1.8.3 Standard analyses and explorations of vital signs data

There is only one study. Not applicable

6.1.8.3.1 Analyses focused on measures of central tendencies

No laboratory data. There is only one study. Not applicable

6.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

No laboratory data. There is only one study. Not applicable

6.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Not applicable.

6.1.8.4 Additional analyses and explorations

Not applicable.

6.1.9 Electrocardiograms (ECGs)

There is only one study. Not applicable because change in ECG measurements (time to 1 mm segment depression) was a secondary efficacy parameter for this study.

6.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results.

There is only one study. Not applicable.

6.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

6.1.9.3 Standard analyses and explorations of ECG data

There is only one study. Not applicable.

6.1.9.3.1 Analyses focused on measures of central tendency

There is only one study. Not applicable.

6.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

There is only one study. Not applicable.

6.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There is only one study. Not applicable.

6.1.9.4 Additional analyses and explorations

There is only one study. Not applicable.

6.1.10 Immunogenicity

Not applicable.

6.1.11 Human Carcinogenicity

Not applicable.

6.1.12 Special Safety Studies

Not applicable.

6.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable.

6.1.14 Human Reproduction and Pregnancy Data

There is only one study. Not applicable.

6.1.15 Assessment of Effect on Growth

There is only one study. Not applicable.

6.1.16 Overdose Experience

See label for other nitrates.

6.1.17 Postmarketing Experience

No studies planned.

Adequacy of Patient Exposure and Safety Assessments

6.1.18 Description of Primary Clinical Data Sources

Populations Exposed and Extent of Exposure Used to Evaluate Safety Study type and design/patient enumeration - See Tables 4, 19 and 22 and pages 8 and 9. Protocol FPC 99-003 and 131-63-11700 were the sources for the primary clinical data. For Demographics See Table 4. There is a distinct lack of females in this study. Otherwise the demographics reflect the defined population. Extent of exposure (dose/duration) See Table 19. There was no evaluation of blood levels of the drug in the subjects studied.

6.1.19 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Publications submitted with NDA.
Other publications. See references.
Case report Forms (crf)
IND 64596 Amendment #2

6.1.19.1 Other studies

There is only one study. Not applicable.

6.1.19.2 Postmarketing experience

Not applicable because this spray is new and it is the first time that butane is being used as a propellant for nitroglycerin.

6.1.19.3 Literature

See references in Section 10.

6.1.20 Adequacy of Overall Clinical Experience

- For this class of drugs, and the relative rarity of patients with chronic stable angina, this reviewer considers that the number of patients studied is adequate when taken in conjunction with literature data. See section on literature review / references

6.1.21 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

6.1.22 Adequacy of Routine Clinical Testing

Post baseline laboratory data are not available.

6.1.23 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

6.1.24 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug;

Not applicable.

6.1.25 Assessment of Quality and Completeness of Data

Considered adequate. Assurance of data quality was adhered to as written in the protocol. Data entry was made using single key entry and then verified against the CRF.

6.1.26 Additional Submissions, Including Safety Update

IND 64596 Amendment #2 has updated the adverse events in second annual report. See Tables 20-22.

Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

See Tables 20-22

General Methodology

6.1.27 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

6.1.27.1 Pooled data vs. individual study data

Not applicable.

6.1.27.2 Combining data

Not applicable.

6.1.28 Explorations for Predictive Factors

Not applicable.

6.1.28.1 Explorations for dose dependency for adverse findings

Not applicable.

6.1.28.2 Explorations for time dependency for adverse findings

Not applicable.

6.1.28.3 Explorations for drug-demographic interactions

Not applicable.

6.1.28.4 Explorations for drug-disease interactions

Not applicable.

6.1.28.5 Explorations for drug-drug interactions

Similar to other nitrates. See label.

6.1.29 Causality Determination

Not applicable.

7 Additional Clinical Issues

Dosing Regimen and Administration

At the onset of an attack one or two metered sprays should be administered into the open mouth. A spray may be repeated approximately every 3 to 5 minutes as needed but no more than 3 sprays are recommended within a 15 minute period. If chest pain persists after a total of 3 sprays medical attention is indicated. Prior to engaging in activities which might precipitate and attack, a spray may be used prophylactically 5-10 minutes before.

During application, the patients should rest in the sitting position and the container held vertically with the spray orifice as close to the mouth as possible. The spray should not be inhaled.

The 0.4 mg dose of the lingual spray was significantly better than the 0.2 mg dose.

The 0.8 mg dose is not statistically significantly better than 0.4mg and shows no significant clinical benefit over the 0.4 mg dose.

Of the three doses, used the most appropriate doses that provide clinical benefit are 0.2 and 0.4 mg although the sponsor selected 0.4 mg as the most appropriate commercial dose.

One dose shall be 3 sprays of 0.4 mg each making a total of 1.2 mg.

Drug-Drug Interactions

See label for nitrates in general. NovaDel's GTN-S is expected to be similar to other nitrate formulations with other drugs. Additive hypotensive effects may occur in patients taking GTN concomitantly with anti-hypertensive drugs, beta-adrenergic blockers, phenothiazines, or calcium channel blockers. Oral administration of GTN increases the oral bioavailability if dihydroergotamine, possibly leading to symptomatic ergotism. GTN is contraindicated in patients using cGMP-specific PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil because it potentiates hypotensive effects of organic nitrates. Intravenous GTN decreases efficacy of tPA and heparin, therefore patients on these drugs should be closely monitored.

Special Populations

Not applicable. Inadequate numbers of patients > 65 years studied.

Pediatrics

Not applicable. No pediatric patients studied.

Advisory Committee Meeting

Not recommended for advisory committee meeting.

Literature Review

Postmarketing Risk Management Plan

Not applicable.

Other Relevant Materials

The use of "stat" in "Nitrostat" that has been approved is already consecrated by long usage and therefore cannot be objected to now. However, '—' should be discouraged in the proposed trade name of this drug as there are no data to support this attribute. DDMAC has commented on the use of these appendages to the proposed trade name and has asked the opinion of the Division.

8 Overall Assessment

Conclusions

The data from this NovaDel-sponsored single study suggest that treatment of patients with chronic stable angina with aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation) results in increase time from start of exercise to development of moderate angina in men (only one female) compared to placebo. The sponsor cannot claim that this happens in females based on one female and based on NovaDel-sponsored trial. Furthermore, aerosol nitrolingual spray (0.2,0.4,0.8 mg per activation), in a dose dependent manner, results in increased time to first onset of angina and in time to 1 mm ST segment depression suggesting an anti-anginal affect based on an anti-ischemic effect. At rest, the expected dose related nitrate effects on heart rates and blood pressure were observed. The ability of subjects to exercise to a higher rate-pressure product provides further support for efficacy. The spray was well tolerated based on the relative ratio-frequencies (RRF) of common adverse events and the relative lack of serious adverse events.

Recommendations on Regulatory Action

- This reviewer recommends approval of this lingual spray using butane as the propellant.
- The only female subject, a 60 year old Caucasian, in the Nova-Del sponsored study had an adverse event suggesting a 100% frequency rate for the gender.
- All subjects were Caucasians suggesting that there were no blacks or other ethnic groups in this study. This is against the regulation that other races should be included in studies.

- The sponsor should not be permitted to use data from other studies since the propellant in other studies is different from butane.

Recommendation on Postmarketing Actions

-  

8.1.1 Risk Management Activity

Not applicable except for females, blacks and other ethnic groups since no information is available.

8.1.2 Required Phase 4 Commitments

8.1.3 Other Phase 4 Requests

Not applicable. 


Labeling Review

- To be added as an addendum.

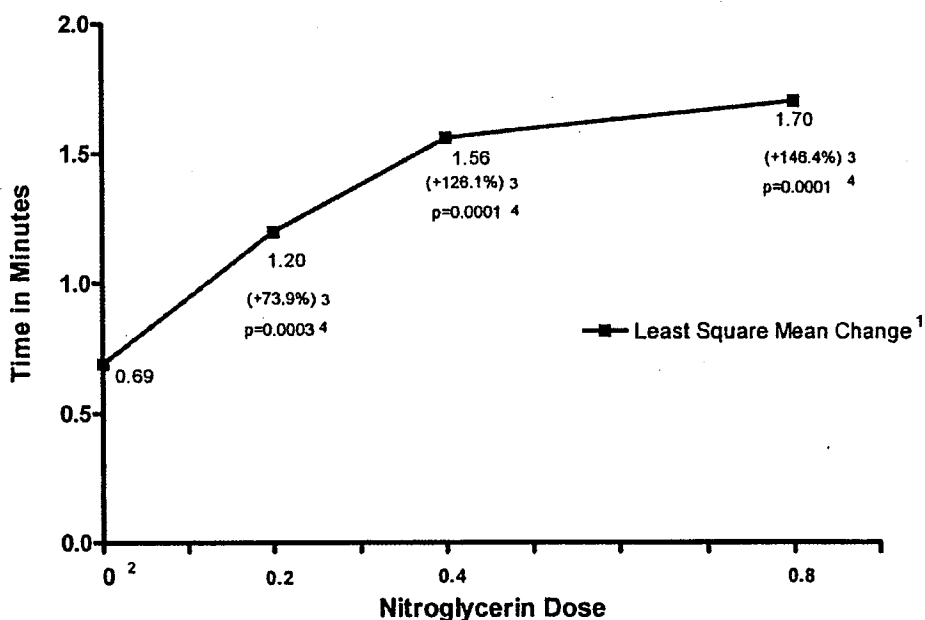
Comments to Applicant

See phase 4 recommendation.

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9 Appendices

Appendix 1: Changes in ETT supplied by sponsor



- 1 Least square mean change for the difference: Investigational Drug ETT – Control (Screening) ETT.
- 2 0 mg represents placebo treatment group.
- 3 Percent change relative to placebo least square mean change.
- 4 P-value for the comparisons of nitroglycerin treatment groups versus placebo.

Appendix 2: Changes in statistical analysis plan

The modifications made to the protocol specified statistical plan were approved by the Division on July 21, 2003, after the data were un-blinded. The modifications provided a much more meaningful and comprehensive evaluation of drug efficacy. The results of the primary efficacy analysis as per protocol were positive and the modifications did not affect the original results.

The primary efficacy endpoint was ETT to the development of moderate angina and the comparisons were to be based on an ANOVA with sequence, subjects within sequence, period and treatment included in the model. The same approach was prespecified for secondary efficacy variables.

In the final analyses, modification of the protocol-specified analysis used a slightly different calculation. Instead of using observed values of ETT during each double-blind treatment period (Table 6) differences between the appropriate ETT and control (screening) ETT were used. This

modification did not change p-values for the between-treatment comparisons. From the statistical perspective, the results of the pair-wise comparisons across nitroglycerin groups provided additional evidence in support of a dose-response trend. The modified planned primary efficacy analysis led to the same conclusions as the protocol-specified statistical evaluation.

Drug supply is in Appendix 3 below.

Appendix 3: Drug Supply - Lot numbers

Drug /Unit(Nitroglycerin)	Route	Lot numbers
0.2mg	Oral	GTN 002
0.4mg	Oral	GTN003
0.8mg	Oral	GTN004
Placebo	Oral	GTN001

Schedule of study procedures is in Appendix 4 below.

Appendix 4: Schedule of study procedures - Double-blind phase of study

		Study day 1		Study Day 2	
Procedure	Screening	Period 1	Period 2	Period 3	Period 4
Informed Consent	X				
Medication and Medical History	X				X
Electrocardiogram	X	X	X	X	X
Vital signs	X	X	X	X	X
Hematology	X				
Chemistry	X				
Urinalysis	X				
Study drug administered		X	X	X	X
Exercise testing	X	X	X	X	X
Blood sample collection	X				

Protocol deviations are in Appendix 5 below.

Appendix 5: Protocol deviations

Subject ID	Deviation
6	Lacks nitrate responsiveness during screening
11	Lacks nitrate responsiveness during screening
14	Failed to reproduce angina.
15	Blood work could not be located
18	Refused blood sampling
26	Blood sample not obtained

Review of Individual Study Reports

- Not applicable because there is only one study.

Line-by-Line Labeling Review

The proposed label is already approved for nitrates/nitrostat. Labeling review is to be agreed with sponsor to reflect current findings in final printed label.

10 References

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