CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208424Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number	208424
Submission Type	505(b)(1)
Submission Date	08-06-2015
Applicant Name	G. Pohl-Boskamp GmbH & Co.KH
Generic Name	Nitroglycerin
Indication	Acute relief of an attack or prophylaxis of angina pectoris
Dosage Form	Oral powder (b) (4)
Dosage Strength	400 µg (b) (4)
OCP Division	Division of Clinical Pharmacology I
OND Division	Cardiovascular and renal products
Primary Reviewer	Venkateswaran Chithambaram Pillai, PhD
Secondary Reviewer	Rajanikanth Madabushi, PhD

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1. EXECUTIVE SUMMARY

In the current new drug application (NDA), G. Pohl-Boskamp GmbH & Co.KH is seeking approval for nitroglycerin (GTN) oral powder in (b) (4) via a 505(b)(1) pathway. The proposed indication is acute relief of an attack or prophylaxis of angina pectoris. Nitrostat® tablets, Nitromist® metered dose aerosol and Nitrolingual® Pumpspray are currently available FDA approved sublingual formulations of GTN in the market.

Pohl-Boskamp has an approved NDA (NDA 18705) for Nitrolingual Pumpspray. It was agreed that Pohl-Boskamp's NDA 18705 could be cross-referenced in the current Nitroglycerin powder NDA (Meeting preliminary comments, Pre IND116608, 01/14/2013).

This review is mainly focused on evaluating the pharmacokinetic (PK) bridging between nitroglycerin oral powder (test) and approved Nitrolingual® Pumpspray (RLD) formulation of nitroglycerin (Study P1302NL) in healthy subjects.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP I) finds the PK bridging acceptable and recommends the approval of nitroglycerin oral powder in (b) (4) formulation from a clinical pharmacology perspective.

1.2 Identify recommended Phase 4 study commitments if the NDA is judged approvable

None.

1.3 Summary of Clinical Pharmacology Findings

- Following sublingual administration of two (b) (4) GTN oral powder each containing 0.4 mg GTN (a total dose of 0.8 mg GTN), GTN oral powder shows higher maximum plasma concentration (C_{max}) (geometric mean ratio (GMR): 2.07-fold) and area under the plasma concentration-time curve ($AUC_{0-\infty}$) (GMR: 1.56-fold) of GTN when compared to 0.8 mg Nitrolingual® Pumpspray. This suggests that the sublingual absorption of GTN is higher following administration of GTN oral powder compared to RLD.
- The systemic exposure to GTN following the administration of GTN oral powder is within the range of previous clinical trial experience with Nitrolingual Pumpspray®.
- No difference in time to reach maximum plasma concentration (T_{max}) or half-life ($t_{1/2}$) is observed between GTN oral powder and RLD.

- Although C_{max} of 1,2-GDN and 1,3-GDN was higher (GMR: 1.43 and 1.34-fold, respectively) following administration of GTN oral powder compared to RLD, the $AUC_{0-\infty}$ and $t_{1/2}$ are similar between both products. The T_{max} of 1,2-GDN and 1,3-GDN occurs slightly earlier for GTN oral powder compared to reference.
- Between subject variability of GTN following administration of test formulation (C_{max}: 68% and $AUC_{0-\infty}$: 78%) is relatively lower than that of RLD (C_{max}: 115% and $AUC_{0-\infty}$: 118%).

2 QUESTION BASED REVIEW (QBR)

Note: The sublingual formulations of nitroglycerin in the market include Nitrostat® tablets, Nitromist® metered dose aerosol and Nitrolingual® Pumpspray. Please refer the package inserts of Nitrostat® tablets, Nitromist® metered dose aerosol and Nitrolingual® Pumpspray for prescribing information, relevant clinical pharmacology literature and clinical studies supporting the proposed indications. Therefore, an abridged version of the question based review is used to address the clinical pharmacology issues pertinent to this drug product.

2.1 General attributes of the drug

2.1.1. What is the background information about drug product?

The drug product consists of an active ingredient nitroglycerin in a powder dosage form (b) (4) (400 µg/ (b) (4) for sublingual administration. The excipients used in this drug product include medium chain triglycerides (b) (4) isomalt (b) (4) anhydrous dibasic calcium phosphate (b) (4), oleoyl polyoxylglycerides (b) (4) and peppermint oil (b) (4) The results of the assay inform that each (b) (4) pack contains 360-440 µg (90-110%) of GTN.

2.1.2. What is the applicant's rationale for developing this drug product?

GTN undergoes extensive first pass metabolism when administered via *per oral* route. Therefore, GTN is commonly administered via sublingual route. Currently the tablets, metered dose aerosol and spray formulations of GTN are available for sublingual administration. Although spray formulation results in rapid increase in plasma concentration of GTN and GDN, the spray must be efficiently delivered under the tongue. In order for delivering GTN in a simple and efficient manner, the oral powder dosage form GTN (b) (4).

2.1.2. What is the regulatory history associated with the submission of this NDA?

The applicant met / communicated with the Division to seek advice on the type of data that would be required for approval of their drug product. Since the plasma exposures of GTN oral powder at 0.4 mg dose is in the range of previously approved GTN formulations at similar dose level and nitroglycerin is titrated to effect, the division recommended that the dose adjustment was not necessary for GTN oral powder. As the exposures following (b) (4) dose of GTN oral powder was expected to be different by only (b) (4)%, the Division suggested that studies should be performed on 0.4 mg rather (b) (4) GTN oral powder.

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Nitroglycerin is a nitric oxide donor which reduces cardiac preload and afterload, myocardial wall tension and oxygen demand through cGMP mediated vasodilatory effects. The proposed indication is acute relief of an attack or prophylaxis of angina pectoris.

2.1.4. What are the proposed dosage(s) and route(s) of administration?

At the onset of an angina attack, up to three (b) (4) packs of 0.4 mg nitroglycerin oral powder will be administered sublingually over a period of 15 minutes. The frequency of dose depends on the intensity of pain perceived by the patient.

2.2 General clinical pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A pivotal PK bridging study, Study P1302NL, was performed to compare the pharmacokinetics, safety and tolerability of nitroglycerin oral powder and nitrolingual pumpspray formulation of nitroglycerin in health volunteers.

Table 1. Design features of the clinical pharmacology study supporting this NDA

Attributes	**Study Elements**
Type of study	Fasting
Design	Single-dose, two-way crossover
Strength	0.4 mg/(b) (4) x 2 (b) (4) (0.8 mg dose)
Subjects	Health males and non-pregnant females (N=32)
Approach	Relative bioavailability study of GTN oral powder vs Nitrolingual Pumpspray (Reference Listed Drug)
Analytes	GTN, 1,2-GDN and 1,3-GDN
Variables	Pharmacokinetics: GTN, 1,2-GDN and 1,3-GDN Safety and tolerability: Adverse events, physical exams, vital signs and safety laboratory

2.3 Basis for regulatory action

2.3.1 What is the basis for regulatory action for this product?

The regulatory action for GTN oral powder (b) (4) is based on the results of a relative bioavailability study P1302NL. The objective of this study was to compare the pharmacokinetics, safety and tolerability of GTN oral powder (Test) and Nitrolingual Pumpspray formulation of nitroglycerin (RLD) in healthy subjects. The GMR (Test/RLD) and 90% confidence interval estimates for C_{max} and $AUC_{0-\infty}$ were computed to evaluate the relative bioavailability of the test formulation compared to the reference.

Relative bioavailability study results: Figure 1 and Table 2 show the comparison of the pharmacokinetics of GTN following sublingual administration of GTN oral powder (test) and Nitrolingual Pumpspray (RLD).

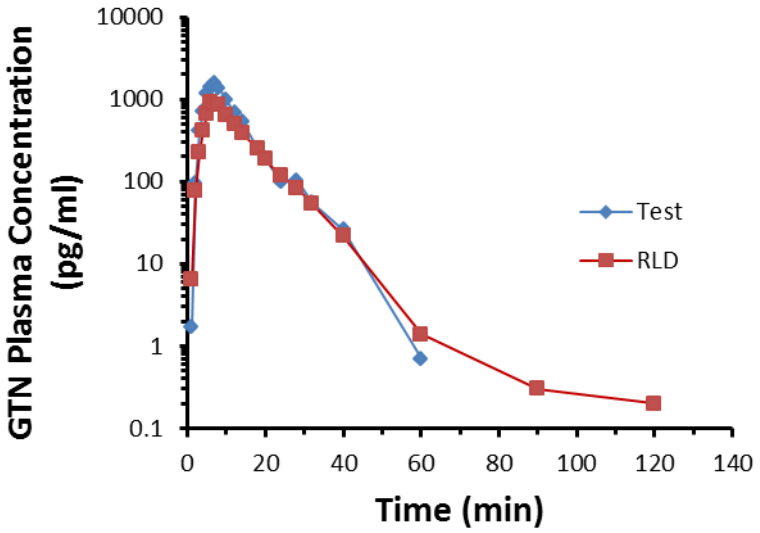

Figure 1. Average plasma concentration-time profile of GTN following sublingual administration of 0.8 mg dose of GTN oral powder and Nitrolingual Pumpspray in healthy subjects.

Table 2. Pharmacokinetic and statistical comparison of GTN following GTN oral powder and Nitrolingual Pumpspray.

Parameter	GMR (Test/RLD) (%)	90% CI	Parameter	Test	RLD
C_{max}	207	159-270	T_{max} (min)	7.0 (3-28)	7.5 (5-28)
$AUC_{0-\infty}$	156	122-200	$T_{1/2}$ (min)	5.6 (48%)	5.9 (98%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

The systemic exposure of GTN is higher (GMR (Test/RLD), C_{max}: 2.07-fold & $AUC_{0-\infty}$: 1.56-fold) following GTN oral powder than Nitrolingual Pumpspray. This suggests that the sublingual absorption of GTN is higher following administration of GTN oral powder compared to RLD. No difference in T_{max} and $t_{1/2}$ is observed between GTN oral powder and RLD. The SE of log transformed GMR for C_{max} and $AUC_{0-\infty}$ are 0.156 and 0.140, respectively. Since these SE values are less than 0.2, the extent of variability in estimating GMR (test/RLD) is considered minimal. Between-subject variability of C_{max} and $AUC_{0-\infty}$ of test formulation (C_{max}: 68% & $AUC_{0-\infty}$: 78%) is relatively lower than that of RLD (C_{max}: 115% & $AUC_{0-\infty}$: 108%).

Figure 2 and Table 3 show the comparison of the pharmacokinetics of 1,2-GDN following sublingual administration of GTN oral powder (test) and Nitrolingual Pumpspray (RLD).

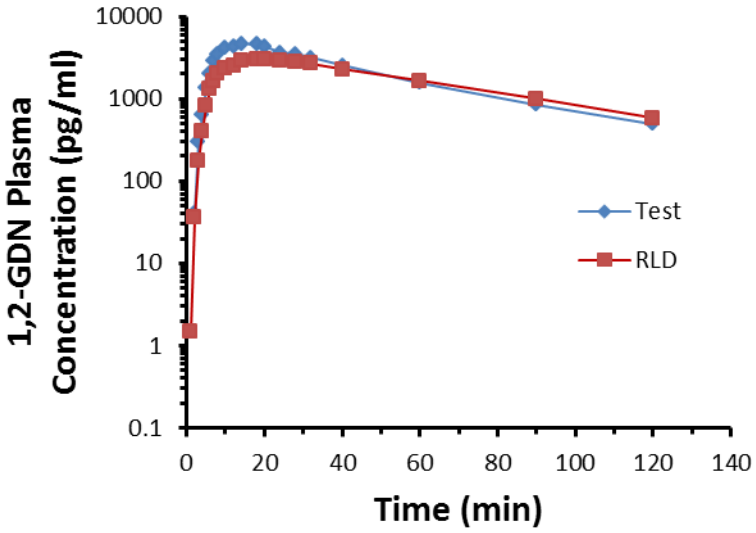

Figure 2. Average plasma concentration-time profile of 1,2-GDN following sublingual administration of 0.8 mg dose of GTN oral powder and Nitrolingual Pumpspray in healthy subjects.

Table 3. Pharmacokinetic and statistical comparison of 1,2-GDN following GTN oral powder and Nitrolingual Pumpspray.

Parameter	GMR (Test/RLD) (%)	90% CI	Parameter	Test	RLD
C_{max}	143	128-159	T_{max} (min)	14 (5-32)	18 (8-60)
$AUC_{0-\infty}$	111	104-119	$T_{1/2}$ (min)	44 (21%)	44 (24%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Although C_{max} of 1,2-GDN is higher (GMR (Test/RLD), C_{max}: 1.43-fold) following GTN oral powder than Nitrolingual Pumpspray, both $AUC_{0-\infty}$ and $t_{1/2}$ are similar for both test and RLD formulations. T_{max} of 1,2-GDN and 1,3-GDN occurs slightly earlier for test formulation compared to RLD. The SE of log transformed GMR for C_{max} and $AUC_{0-\infty}$ are 0.063 and 0.039, respectively. Since these SE values are less than 0.2, the extent of variability in estimating GMR (test/RLD) is considered minimal. Between-subject variability of C_{max} and $AUC_{0-\infty}$ of test formulation (C_{max}: 39% & $AUC_{0-\infty}$: 24%) is relatively lower than that of RLD (C_{max}: 46% & $AUC_{0-\infty}$: 32%).

Figure 3 and Table 4 show the comparison of the pharmacokinetics of 1,3-GDN following sublingual administration of GTN oral powder (test) and Nitrolingual Pumpspray (RLD).

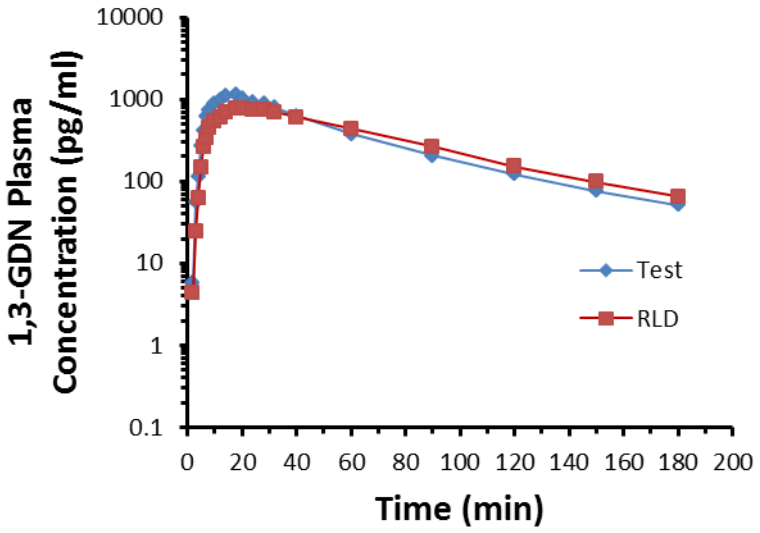

Figure 3. Average plasma concentration-time profile of 1,3-GDN following sublingual administration of 0.8 mg dose of GTN oral powder and Nitrolingual Pumpspray in healthy subjects.

Table 4. Pharmacokinetic and statistical comparison of 1,3-GDN following GTN oral powder and Nitrolingual Pumpspray.

Parameter	GMR (Test/RLD) (%)	90% CI	Parameter	Test	RLD
C_{max}	134	119-151	T_{max} (min)	16 (5-40)	24 (10-90)
$AUC_{0-\infty}$	105	97-113	$T_{1/2}$ (min)	45 (20%)	45 (22%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Despite a higher C_{max} of 1,3-GDN (GMR (Test/RLD), C_{max}: 1.34-fold) following GTN oral powder than Nitrolingual Pumpspray, both $AUC_{0-\infty}$ and $t_{1/2}$ are similar for both test and RLD formulations. T_{max} of 1,2-GDN and 1,3-GDN occurs slightly earlier for test formulation compared to RLD. The SE of log transformed GMR for C_{max} and $AUC_{0-\infty}$ are 0.069 and 0.044, respectively. Since these SE values are less than 0.2, the extent of variability in estimating GMR (test/RLD) is considered minimal. Between-subject variability of C_{max} and $AUC_{0-\infty}$ of test formulation (C_{max}: 40% & $AUC_{0-\infty}$: 26%) is relatively lower than that of RLD (C_{max}: 50% & $AUC_{0-\infty}$: 32%).

In a nutshell, the systemic exposure of GTN is higher following GTN oral powder than Nitrolingual pumpspray. There is no difference in the time to reach maximum systemic exposure of GTN between GTN oral powder and Nitrolingual Pumpspray. The standard error around log transformed geometric mean ratios for C_{max} and $AUC_{0-\infty}$ of GTN and its metabolites (1,2-GDN and 1,3-GDN) are less than 0.2 which suggests the extent of variability in estimating geometric mean ratios (test/RLD) is considered minimal. The between subject variability in C_{max} and $AUC_{0-\infty}$ for GTN oral powder is relatively lower than that of RLD.

The increased systemic exposure with GTN oral powder is covered by the previous clinical trial experience with Nitrolingual Pumpspray®. Dose dependant increase in exercise tolerance, time to onset of angina and ST-segment depression were seen

following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pumpspray as compared to placebo. The drug showed a profile of mild to moderate adverse events. As such the increased exposure with GTN oral powder is not expected to result in altered efficacy or safety profile compared to Nitrolingual Pumpspray®. Further, given the short half-life of nitroglycerin and dosing instructions to titrate till relief of chest pain (up to a maximum of 1200 mcg in 15 minutes over 5 minutes intervals) provides a strategy for safe use of GTN oral powder. Therefore, the efficacy and safety of GTN oral powder is expected to be similar to Nitrolingual Pumpspray®.

2.4 Bioanalytical Methods

Plasma concentration of GTN, 1,2-GDN and 1,3-GDN were measured by validated GC/MS assay. It was found that:

- The inter-day and intra-day precision and accuracy values of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were equal to or better than 15% (20% at the LLOQ).
- GTN, 1,2-GDN and 1,3-GDN samples were found to be stable in plasma after 1 h when placed in an ice-bath and after 1 freezing/thawing cycle. The analytes in the prepared samples were stable for atleast 24 h at room temperature or under autosampler conditions (~10˚C) for atleast 4 days.
- The QC sample accounting for dilution showed no bias. Although there was no carry over effect observed with GTN, the metabolites, 1,2-GDN and 1,3-GDN showed a significant carry over effect. Appropriate measures were taken to overcome the carry over effects.
- More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable.

Note: Bioanalysis of GTN, 1,2-GDN and 1,3-GDN from Study P1302NL were performed at (b) (4). Because of the PK results from Study P1302NL was critical to this NDA, OCP requested an inspection of the bioanalytical site via Office of Scientific Investigations (OSI) on (b) (4). As per the findings from the last inspection of the bioanalytical site, OSI has recommended us to accept the data without onsite inspection.

3 APPENDIX

3.1 Clinical pharmacology and biopharmaceutics individual study review

CLINICAL PHARMACOLOGY REVIEW
Biopharmaceutics – Bioavailability / Bioequivalence

Study #: P1302NL	**Study Period:** 19 February 2014 – 21 March 2014
Study Site: [redacted] (b) (4)	**Investigator:** Michael Lissy

Title	A randomized, controlled, open, crossover study in healthy volunteers to describe and compare the in vivo biopharmaceutical properties of an investigational nitroglycerin oral powder.
Rationale	GTN undergoes extensive first pass metabolism when administered via *per oral* route. Therefore, GTN is commonly administered via sublingual route. Currently the tablets, metered dose aerosol and spray formulations of GTN are available for sublingual administration. Although spray formulation results in rapid increase in plasma concentration of GTN and GDN, the spray must be efficiently delivered under the tongue. In order for delivering GTN in a simple and efficient manner, the oral powder dosage form GTN [redacted] (b) (4).

Study Design

☐ Bioequivalence	☐ Absolute Bioavailability	☑ Relative Bioavailability

Dose **Two** [redacted] (b) (4) **packs** Randomization **Yes** Blinding **No** Type **Fasting** Center **Single**
Period **Two** Population **Healthy volunteers**

	Length (Days)	In Clinical Unit (Yes/No)
Screening	-21 to -1	No
Period	2	Yes
Washout	3	No

Treatments: (Active Ingredients: GTN, 1,2-GDN and 1,3-GDN)

	Test	Reference
Dosage Form	Oral powder	Pumpspray
Dosage Strength	0.8 mg	0.8 mg
Batch #	228695	230828
Administration	Sublingual	Sublingual

☑ Fast ☐ Fed ☐ With Water ☑ Without Water

Interfering Substances Excluded	Not applicable
Sampling Times	0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 20, 24, 28, 32, 40, 60, 90, 120, 150 and 180 min
PK Parameters	C_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$
Statistical/PK Analysis	The pharmacokinetic parameters of test and reference formulations of nitroglycerin are compared by means of geometric mean ratio (Test/RLD) and 90% confidence interval estimates for C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$. The ANOVA is performed to evaluate the effects of period, treatment, sequence and subjects within sequence on the pharmacokinetic parameters, C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$. The standard error (SE) of treatment difference is obtained from the ANOVA of the log transformed pharmacokinetic parameters.

Analytical Method

Method Type	GC/MS	Matrix	Plasma
Analytes	GTN	1,2-GDN	1,3-GDN
Calibration range (pg/ml)	5-5000	20-20000	10-10000

Precision [CV (%)]	≤7.7%	≤8.5%	≤11.0%
Bias (%)	≤13.8%	≤13.3%	≤7.0%
Sensitivity [LLOQ (pg/ml)	5	20	10

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Reviewer's comments: Bio-analytical method validation and sample analysis results are acceptable.

Results

Study Population

Randomized	Yes
Treated	32
Completed	32
Discontinued Due to AE	0
PK Population/Safety Population	32/32
Age [Median (range)]	41.5 (23-52)
Male/Female	13/19
Race (Caucasian/Black/Asian/Hispanic)	Caucasian: 31 & Black: 1

Pharmacokinetics

Geometric Mean Ratio & 90% CI (Test/Reference) of the pharmacokinetic parameters of GTN, 1,2-GDN and 1,3-GDN are shown below:

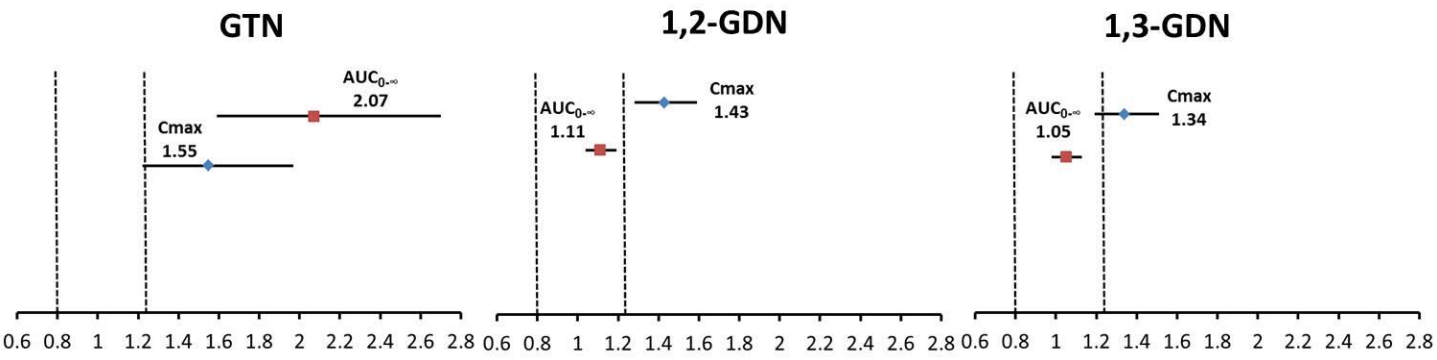

Figure 1 represents the geometric mean ratio (Test/Reference) for area under the plasma concentration-time curve ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) of GTN, 1,2-GDN and 1,3-GDN in healthy volunteers. The error bars represent the 90% CI around GMR.

Pharmacokinetic Parameters

Table 1. Pharmacokinetic parameters of GTN following GTN oral powder and Nitrolingual Pumpspray.

Parameter	Geometric mean (% CV)	
	Test	RLD
C_{max} (pg/ml)	1666 (67.9)	804 (114.9)
AUC_{0-Last} (pg.min/ml)	12253 (76.5)	7897 (110.7)
$AUC_{0-\infty}$ (pg.min/ml)	12112 (78.3)	8087 (107.5)
T_{max} (min)	7.0 (3-28)	7.5 (5-28)
$T_{1/2}$ (min)	5.6 (48%)	5.9 (98%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Between subject variability of GTN following administration of test formulation (C_{max}: 68% and $AUC_{0-\infty}$: 78%) is relatively lower than that of RLD (C_{max}: 115% and $AUC_{0-\infty}$: 118%)

Table 2. Pharmacokinetic parameters of 1,2-GDN following GTN oral powder and Nitrolingual Pumpspray.

Parameter	Geometric mean (% CV)	
	Test	RLD
C_{max} (pg/ml)	4910 (38.6)	3435 (46.4)
AUC_{0-Last} (pg.min/ml)	238612 (23.7)	207572 (32.2)

$AUC_{0-\infty}$ (pg.min/ml)	248768 (24.1)	227086 (31.5)
T_{max} (min)	14 (5-32)	18 (8-60)
$T_{1/2}$ (min)	44 (21%)	44 (24%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Between subject variability of 1,2-GDN following administration of test formulation (C_{max}: 39% and $AUC_{0-\infty}$: 24%) is lower than that of RLD (C_{max}: 46% and $AUC_{0-\infty}$: 32%)

Table 3. Pharmacokinetic parameters of 1,3-GDN following GTN oral powder and Nitrolingual Pumpspray.

Parameter	Geometric mean (% CV)	
	Test	RLD
C_{max} (pg/ml)	1193 (39.7)	887 (49.7)
AUC_{0-Last} (pg.min/ml)	57734 (24.4)	53359 (32.6)
$AUC_{0-\infty}$ (pg.min/ml)	61099 (25.5)	58275 (32.3)
T_{max} (min)	16 (5-40)	24 (10-90)
$T_{1/2}$ (min)	45 (20%)	45 (22%)

T_{max}: median (range) ; $T_{1/2}$: arithmetic mean (CV %)

Between subject variability of 1,3-GDN following administration of test formulation (C_{max}: 40% and $AUC_{0-\infty}$: 26%) is relatively lower than that of RLD (C_{max}: 50% and $AUC_{0-\infty}$: 32%)

Pharmacokinetic Profile

Average plasma concentration-time profiles of GTN, 1,2-GDN and 1,3-GDN following GTN oral powder and Nitrolingual Pumpspray are shown in the following figure.

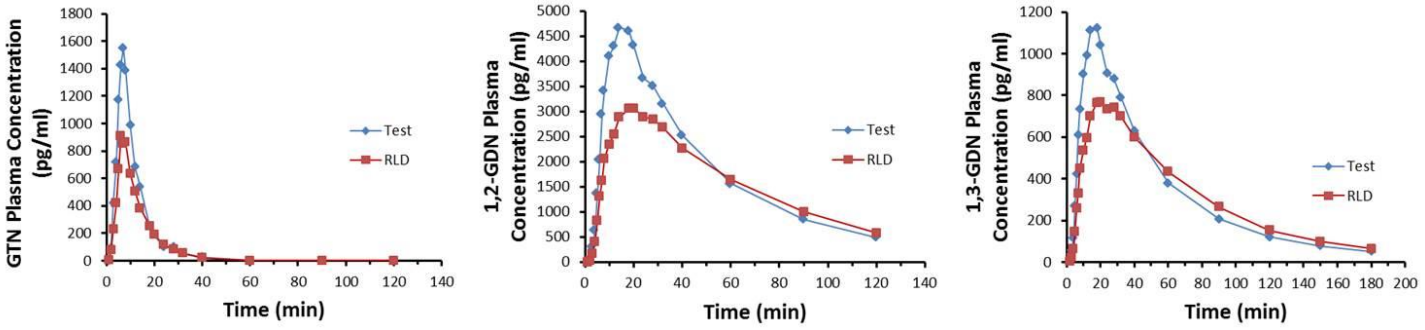

Figure 2 Mean plasma concentration-time profiles of test and reference formulation of GTN and its metabolites, 1,2-GDN and 1,3-GDN in healthy subjects are plotted in linear scale.

Reviewers' comments: PK sampling and data analysis are acceptable. Test formulation shows higher C_{max} and $AUC_{0-\infty}$ of GTN than RLD. This suggests that the sublingual absorption of GTN is higher following administration of GTN oral powder compared to Nitrolingual Pumpspray. However, the systemic exposure to

GTN following administration of GTN oral powder is within the range of previous clinical trial experience with Nitrolingual Pumpspray®. Dose dependant increase in exercise tolerance, time to onset of angina and ST-segment depression were seen following doses of 0.2, 0.4, 0.8 and 1.6 mg of nitroglycerin delivered by metered pumpspray as compared to placebo. The drug showed a profile of mild to moderate adverse events. Both T_{max} and $t_{1/2}$ of GTN are similar for both test and RLD formulations. Between subject variability of C_{max} and $AUC_{0-\infty}$ of test formulation is relatively lower than that of RLD.

Site Inspection

Requested: ☑ Yes ☐ No **Performed:** ☐ Yes ☑ No ☐ NA

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

The current study characterizes the relative bioavailability of GTN oral powder compared to Nitrolingual Pumpspray® when administered via sublingual route providing the PK bridge information. The increased systemic exposure with GTN oral powder is not expected to result in altered efficacy or safety profile compared to Nitrolingual Pumpspray®. Further, given the short half-life of nitroglycerin and dosing instructions to titrate till relief of chest pain (up to a maximum of 1200 mcg in 15 minutes over 5 minutes intervals) provides a strategy for safe use of GTN oral powder. Therefore, the efficacy and safety of GTN oral powder is expected to be similar to Nitrolingual Pumpspray®.

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/s/

VENKATESWARAN CHITHAMBARAM PILLAI
06/01/2016

RAJANIKANTH MADABUSHI
06/01/2016
This the final clinical pharmacology review and replaces the review in DARRTS dated 04/04/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208424	**SDN**	1
Applicant	Pohl Boskamp GmbH & Co	**Submission Date**	08/10/2015
Generic Name	Nitroglycerin	**Brand Name**	GoNitro [proposed]
Drug Class	Vasodilator		
Indication	Acute relief of an attack or prophylaxis of angina pectoris		
Dosage Regimen	Acute: Up to 3 (b) (4) within 15 min for acute relief; Prophylaxis: Use 5-10 min prior to engaging in activities that might precipitate an acute attack		
Dosage Form	400 µg nitroglycerin powder (b) (4)	**Route of Administration**	Oral
OCP Division	I	**OND Division**	Cardiovascular and Renal Drug Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Venkateswaran Chithambaram Pillai	Rajanikanth Madabushi
Pharmacometrics	--	--
Genomics	--	--

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	10/9/2015	**74-Day Letter Date**	10/23/2015
Review Due Date	4/5/2016	**PDUFA Goal Date**	6/10/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

Comment: This is a routine inspection for the bioanalytical aspects [method validation and bioanalysis of test samples] of the study which forms the basis for PK bridge. The inspection request to Office of Study Integrity and Surveillance (OSIS) was sent on 10/08/2015.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		

☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		1	P1302NL
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above	☑Yes ☐No ☐N/A	Currently, subject level plasma concentration data and corresponding PK measures is available in a 'pdf' file. An information request was sent asking the dataset as SAS transport files. The applicant agreed to send the datasets by 10/16/2015.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No',	☑Yes ☐No ☐N/A	See comment to Q7

has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VENKATESWARAM CHITHAMBARAM PILLAI
10/14/2015

RAJANIKANTH MADABUSHI
10/14/2015