

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-504**

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



## 1 Executive Summary

Vyteris, Inc. has originally submitted NDA 21-504 for the Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar System) on 9/25/02. On 7/25/03, the Applicant was sent an approvable action letter and the Agency's labeling (package insert) comments. In response to the Agency's action letter and labeling comments, the Applicant has submitted the current Amendment #020, which includes the responses to all the deficiencies and the labeling comments. This review will address the Question #26 and provide comments on the Applicant's new labeling proposal.

In the Letter, the Applicant was asked to address the bioequivalence requirement (Item #26),

### Item #26:

Your application states that bioequivalence requirements were waived. Provide information on this waiver and against which product requirements were waived.

The Applicant's Response:

### Response to Item 26:

The reference to bioequivalence requirements was related to the comparability of the pilot and commercial product based on there being no changes in the process or formulation during scale-up. Vyteris believes that bioequivalence is not required. (End of Phase II Meeting held on February 17, 2000, Dr. Uppoor stated that, "if the pilot and commercial-scale products are considered comparable upon review, then there is no need for a bioequivalency study"). At that time no conclusions could be made without NDA review.

The process used to manufacture Phase III supplies and the commercial process use the same equipment, materials, and formulation. The batch sizes of the anode and cathode solution mixes were 100% of the commercial batch size. The batch size of the patches manufactured for Phase III and primary stability were 25% of the commercial batch size ( — patches). Based on the Phase III and commercial manufacturing processes being the same, Vyteris believes bioequivalence requirements are not required.

### Reviewer's Comment:

Above bioequivalence (BE) question can be interpreted to have two distinct questions :

1. BE regarding clinical trial vs. to-be-marketed formulations

The Applicant's response relating to Dr. Upoor's comment is appropriate. Additionally, the PK and pivotal clinical studies were conducted with the to-be-marketed formulation. Therefore, there are no issues with this question.

**2. BE regarding LidoSite to-be-marketed formulation vs. Reference Listed Drug (RLD) product**

The Applicant did not answer this question per se, however, the comparison of LidoSite to RLD, based on the lidocaine and epinephrine, may be difficult to do, since there were no systemic lidocaine and epinephrine levels observed in pharmacokinetic studies. Therefore, there are no issues with this question.

Overall, there are no further pending issues found in this application.

**1.1 Recommendations**

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the Amendment submitted on 11/8/03.

From OCPB point of view, the information contained in the Amendment is acceptable. There are no further pending issues with the application at this time.

David J. Lee, Ph.D.  
Clinical Pharmacologist, DPE2/OCPB

Suresh Doddapaneni, Ph.D.  
Team Leader, DPE2/OCPB

**1.2 Phase IV Commitments**

Not applicable.

**1.3 Summary of CPB Findings**

Not applicable. No new information was submitted in the current amendment.

**2 QBR**

**2.1 General Attributes of the Drug** - Not applicable.

**2.2 General Clinical Pharmacology**- Not applicable.

**2.3 Intrinsic Factors-** Not applicable.

**2.4 Extrinsic Factors-** Not applicable.

**2.5 General Biopharmaceutics**

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

In the Letter, the Applicant was asked to address the bioequivalence requirement (Item #26),

Item #26:

Your application states that bioequivalence requirements were waived. Provide information on this waiver and against which product requirements were waived.

The Applicant's Response:

Response to Item 26:

The reference to bioequivalence requirements was related to the comparability of the pilot and commercial product based on there being no changes in the process or formulation during scale-up. Vyteris believes that bioequivalence is not required. (End of Phase II Meeting held on February 17, 2000, Dr. Upoor stated that, "if the pilot and commercial-scale products are considered comparable upon review, then there is no need for a bioequivalency study"). At that time no conclusions could be made without NDA review.

The process used to manufacture Phase III supplies and the commercial process use the same equipment, materials, and formulation. The batch sizes of the anode and cathode solution mixes were 100% of the commercial batch size. The batch size of the patches manufactured for Phase III and primary stability were 25% of the commercial batch size ( — patches). Based on the Phase III and commercial manufacturing processes being the same, Vyteris believes bioequivalence requirements are not required.

**Reviewer's Comment:**

Above bioequivalence (BE) question can be interpreted to have two distinct questions :

1. BE regarding clinical trial vs. to-be-marketed formulations

The Applicant's response relating to Dr. Upoor's comment is appropriate. Additionally, the PK and pivotal clinical studies were conducted with the to-be-marketed formulation. Therefore, there are no issues with this question.

2. BE regarding LidoSite to-be-marketed formulation vs. Reference Listed Drug (RLD) product

The Applicant did not answer this question per se, however, the comparison of LidoSite to RLD, based on the lidocaine and epinephrine, may be difficult to do, since there were no systemic lidocaine and epinephrine levels observed in pharmacokinetic studies.

With respect to comparing controllers and the patch sizes (a controller manages the current, which is related to the amount of lidocaine and epinephrine delivery), the CMC Review (or 510K application review) should provide information. Therefore, there are no issues with this question.

**2.6 Analytical Section - Not applicable**

**3 Detailed Labeling Recommendations**

The proposed Agency's Clinical Pharmacology labeling language has been accepted by the Applicant. There are no further unresolved issues regarding labeling.

**4 Appendices**

4.1 Proposed Package Insert (Counter proposal by the Applicant)



13 Page(s) Withheld

\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_ § 552(b)(5) Deliberative Process

✓  
\_\_ § 552(b)(4) Draft Labeling

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

/s/  
-----

David Lee  
2/27/04 11:39:36 AM  
BIOPHARMACEUTICS

Suresh Doddapaneni  
2/27/04 11:40:58 AM  
BIOPHARMACEUTICS



The Applicant has submitted 4 studies under the Clinical Pharmacology section of the NDA. To-be-marketed formulation was used in 3 studies: studies BDTS-99-56, BDTS-00-10 and Vyteris 01-01; however, Study 98NS01-8 utilized the MIP II delivery system, the precursor to MIP III.

#### Lidocaine

Plasma samples from Study 98NS-01-08 were contaminated, due to sampling error. Additionally, this study utilized MIP II delivery system. Thus, the results from this study were not considered critical.

Studies BDTS-99-56 and BDTS-00-10 indicated that plasma samples were below the limit of quantitation for lidocaine (LC/MS analytical method; LOQ was 5 ng/mL). Thus, no pharmacokinetic parameters were calculated.

Generally, a lidocaine blood level greater than 1.5 µg/mL is generally considered to have systemic pharmacologic effect in a clinical setting, while a level greater than 6 µg/mL is considered toxic.

#### Epinephrine

Study Vyteris 01-01 results indicated that no subject had an epinephrine concentration above 50 pg/mL (normal range, 5-50 pg/mL; HPLC analytical method with electrochemical detection with a limit of detection of 10 pg/mL), indicating that the Northstar MIP III did not provide additional epinephrine to the systemic circulation.

### 1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed the original NDA 21-504 submitted on 05/09/02.

From OCPB point of view, the information contained in the NDA is acceptable provided that the Agency and the Applicant can come to a mutual agreement with respect to the language in the package insert (see section 5 of this review).

David J. Lee, Ph.D.  
Clinical Pharmacologist  
DPE2/OCPB

Suresh Doddapaneni, Ph.D.  
Team Leader, DPE2/OCPB

## 2 Table of Contents

<b>1</b>	<b>Executive Summary.....</b>	<b>1</b>
1.1	Recommendation	2
<b>2</b>	<b>Table of Contents.....</b>	<b>3</b>
<b>3</b>	<b>Summary of CPB Findings .....</b>	<b>3</b>
<b>4</b>	<b>QBR.....</b>	<b>5</b>
4.1	General Clinical Pharmacology	5
4.2	General Biopharmaceutics	6
<b>5</b>	<b>Labeling.....</b>	<b>6</b>
<b>6</b>	<b>Appendix.....</b>	<b>10</b>
6.1	Proposed labeling	10
6.2	Individual Study Synopsis	21

## 3 Summary of CPB Findings

To measure plasma lidocaine concentrations, three studies were performed in human subjects. Two of these studies [BDTS-99-56 in adult subjects (13 male/female adult subjects at ages 26-57 years) and BDTS-00-10 in pediatric subjects (12 male/female pediatric subjects at ages 6-15 years)] utilized the MIP III delivery system, and one study (98NS01-8, 13 healthy male/female subjects, 19-44 years) utilized the Northstar MIP II patch, a precursor to MIP III. The current delivery cycle for the iontophoresis was 10 minutes for each application. Studies BDTS-99-56 and BDTS-00-10 were single center, randomized, repeat application, open-label, Phase I studies (randomly assigned to receive patch applications at a single visit at three of the following four application sites: upper chest, upper back, dorsum of the hand, and antecubital fossa; separate patches were applied in sequence at 0, 3, and 3.5 hours at the different sites with removal of patches prior to the repeat application) and Study 98NS01-8 was a randomized, open-label, crossover, single-center study.

To measure plasma epinephrine concentrations, a randomized, crossover, single-center study in 29 healthy male/female subjects, 17-61 years old, (Vyteris 01-01) was performed using the Northstar MIP III. A patch that contained only lidocaine was used as a comparative patch.

### Safety findings

Studies 98NS-01-08 (second part only; ECGs in 3 subjects at the screening visit and then at 1 to 3 hours following treatment) and Vyteris-01-01 (30 and 15 minutes prior to and at 10, 30, and 60 minutes following each treatment) included ECG recordings as a safety evaluation. There were no clinically significant changes to ECGs noted in any of the 3 subjects from Study 98NS-01. Additionally, there were no notable differences between the 2 treatments in the percentage of abnormal ECGs at any time-point in Study Vyteris-01-01.

No systemic adverse effects were reported. No clinically significant skin effects were reported.

### Pharmacokinetic findings

Plasma lidocaine concentrations were measured using a validated LC/MS analytical method (LOQ was 5 ng/mL).

Plasma epinephrine concentrations were measured using a HPLC analytical method with electrochemical detection with a limit of detection of 10 pg/mL.

#### Lidocaine

For Studies BDTS-99-56 and BDTS-00-10, all collected samples were below the limit of quantitation for lidocaine. However, there were two cases which lidocaine levels were observed: In one case, the baseline sample was diluted during processing to accommodate a low sample volume and the dilution process produced an inability to quantify the lidocaine level below 10 ng/mL. In the second case, in another subject a quantifiable plasma lidocaine level ( ng/mL) was observed in the sample collected immediately after the third exposure to the patch. Lidocaine levels were again lower than the LOQ at subsequent samples, 15 minutes later. Thus, no pharmacokinetic parameters were calculated.

Generally, a blood level greater than 1.5 µg/mL is generally considered to have systemic therapeutic effect in a clinical setting, while a level greater than 6 µg/mL is considered toxic.

For Study 98NS-01-08, all concentrations of lidocaine obtained during the initial part of the study were below the LOQ with the exception of four samples, which were due to sampling error (samples obtained underneath the iontophoretic patch site), leading to contamination of the samples (For one subject (#006) the 3-hour concentration of lidocaine was reported as ~ µg/mL. For a second subject (#010) the 0.92 (55 minute)-hour sample was reported as ~ µg/mL; the 1.5-hour sample was ~ µg/mL, and the 3-hour sample was ~ µg/mL. The concentrations for all other times for subjects 006 and 010 were below the LOQ for lidocaine.).

#### Epinephrine

For both treatments (Northstar MIP III and lidocaine comparator arms) no subject had an epinephrine concentration above 50 pg/mL (normal range, 5-50 pg/mL) in the study, indicating that the Northstar MIP III did not provide additional epinephrine to the systemic circulation.

### Literature Review for comparison

Theoretically, during a single 10-minute treatment of 17.7 mA•min, approximately 547 µg of lidocaine and 6.2 µg of epinephrine are delivered to the skin with no evidence of systemic absorption. In the clinical setting this translates to a dose of lidocaine of 7.8 µg/kg or 54.7 µg/kg for a 70 kg person or a 10 kg child, respectively, and to a dose of epinephrine of 0.09 µg/kg and 0.62 µg/kg for a 70 kg person or a 10 kg child, respectively.

It is noted that the recommended maximum dose for normal healthy adults for lidocaine HCl with or without epinephrine should not exceed 7 mg/kg or 4.5 mg/kg, respectively. For children of 5 years with normal body mass and development weighing 50 lbs, the recommended dose of lidocaine should not exceed 75 – 100 mg (3.3 – 4.4 mg/kg). (Lidocaine Package Insert)

The usual dose of epinephrine for allergic emergencies for adults is 0.3 mg and for pediatric use is 0.15 – 0.3 mg. (Epinephrine Package Insert). Fisher et al (1993) gave children (8.5-47.1 kg) in hemodynamic shock, intravenous epinephrine infusions of 0.2 to 0.3 µg/kg/minute. At a minimum, these children received 2 µg /kg intravenously over ten minutes, an amount moderately in excess of that delivered by the Northstar System. Mean plasma concentrations of  $4360 \pm 3090$  pg/mL were reported.

On the contrary, the data from the four pharmacokinetic studies, no measurable levels of lidocaine were observed in plasma, and epinephrine plasma levels were within the normal range.

## **4 QBR**

### **4.1 General Clinical Pharmacology**

#### **What is the pharmacological class for lidocaine and epinephrine?**

Lidocaine is a local anesthetic that works by selectively binding to sodium ion channels thereby slowing down depolarization of nerve cell membranes. Lidocaine is rapidly de-ethylated to the active metabolite which is then hydrolyzed by amidases to various components that have reduced activity. Approximately 90% of lidocaine is excreted in the form of various metabolites and less than 10% of a dose is excreted unchanged via the kidneys.

Epinephrine is a naturally occurring endocrine compound secreted by the adrenal medulla into the circulatory system, essential in the neuro-humoral transmission of the sympathetic nervous system. It is a potent stimulator of both alpha and beta-adrenergic receptors with a complex set of observable responses. Systemically, epinephrine has been used as a bronchodilator for bronchospastic disease. Locally, epinephrine has been used as a vasoconstrictor. Most exogenously administered or endogenously released epinephrine is very quickly inactivated by uptake into adrenergic neurons, diffusion, plasma protein binding and enzymatic degradation in the liver and body tissues. Enzymes responsible for the inactivation of epinephrine are catechol-O- methyltransferase (COMT) and monamine oxidase (MAO). Metabolites are excreted in the urine mainly as glucuronide or sulfate ether conjugates. Epinephrine does not reach pharmacologically active concentrations in the body after oral administration because it is destroyed in the gastrointestinal tract and rapidly conjugated and oxidized in the liver.

**Is there a safety concern with lidocaine exposure from Northstar delivery system?**

No, the results from the studies indicated that lidocaine concentrations were not observed in pediatrics and adults post Northstar system administration.

**Is there a concern with epinephrine exposure from Northstar delivery system?**

No, the results from the studies indicated that observed epinephrine concentrations in adults were within the normal range (5-50 pg/mL) post Northstar system administration.

**4.2 General Biopharmaceutics**

Anode formulation:

The quantitative composition of the drug components/excipients which make up the Anode formulation containing lidocaine hydrochloride, USP and (-) epinephrine (+) bitartrate, USP as the active drug substances is as follows:

<u>Component</u>	<u>mg per Patch</u>
Lidocaine hydrochloride, USP	100.0
(-) Epinephrine (+) bitartrate, USP	1.91
Glycerin, USP	
Sodium metabisulfite, NF	
Edetate disodium, USP	
Citric acid, USP	
Sodium chloride, USP	

Placebo Anode formulation:

Lidocaine hydrochloride, USP	0.0
(-) Epinephrine (+) bitartrate, USP	1.91
Glycerin, USP	
Sodium metabisulfite, NF	
Edetate disodium, USP	
Citric acid, USP	
Sodium chloride, USP	

Cathode and Placebo Cathode formulation:

The quantitative composition of the excipients which make up the Cathode Gel is as follows:

<u>Component</u>	<u>mg per patch</u>
Sodium chloride, USP	
Glycerin, USP	
Monobasic Sodium Phosphate, USP	

**5 Labeling**

The Applicant's Labeling is revised with ~~strikeouts~~ and inserts.

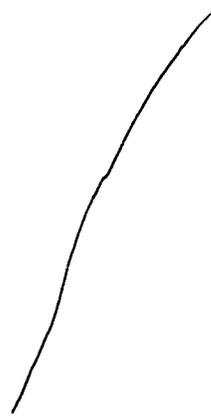
The following revised labeling should be forwarded to the Applicant as appropriate.

14 Page(s) Withheld

— § 552(b)(4) Trade Secret / Confidential

— § 552(b)(5) Deliberative Process

✓  
— § 552(b)(4) Draft Labeling



## 6.2 Individual Study Synopsis

### **Phase I Study: A Pharmacokinetic Study to Determine Plasma Concentrations of Lidocaine Following Use of the Northstar Iontophoretic Lidocaine Drug Delivery System in Adult Subjects (BDTS-99-56)**

#### *Design, Objective, and Number of Subjects*

This was an open-label, randomized, repeat-application, single-center study of the Northstar system (MIP III, a TBM formulation). The objective of this study was to determine plasma concentrations of lidocaine following single and repeat treatment with the Northstar System in adult subjects. A total of 13 subjects who were at least 18 years of age were enrolled.

#### *Methodology*

Subjects were randomly assigned to receive an application of the Northstar system (100 mg of lidocaine HCl and 1.05 mg of epinephrine delivered with a delivered with a 3.4 mA-min/cm<sup>2</sup> charge density, a total charge of 17 mC/min) administered over 10 minutes at 3 of 4 application sites: upper chest, upper back, dorsum of the hand, and antecubital fossa. Treatments were delivered in sequence, at t=0, t=180 and t=210 minutes. Blood samples were collected before treatment, and at 15, 30, 60, 120, 175, 205, 225, 240, 270, 400, and 580 minutes following treatment, where t = 0 is the time of first application/activation of the Northstar system, and analyzed for plasma levels of

lidocaine. Plasma lidocaine concentrations were measured by the central lab using a validated LC/MS analytical method (LOQ was 5 ng/mL). Each subject was evaluated for erythema, and edema using the Draize scale immediately following treatment and at 24 □4 hours following each treatment and for blanching at 15, 205, and 225 minutes following each treatment. All subjects were monitored for adverse events.

### ***Statistical Method***

ANOVA was used as the primary analysis after the single and repeat applications. Standard noncompartmental pharmacokinetic analyses were performed on the 12 blood samples for each subject. It was expected that no lidocaine would be detected after 1 hour post-treatment, and that only very minute amounts near the limit of detection (5 ng or less) would be found between time 0 and 1 hour. If lidocaine was detected only up to 1 hour post-treatment, then 95% confidence intervals would have been constructed for mean plasma lidocaine at each time point for which lidocaine was detected. A p-value of less than 0.05 is considered statistically significant.

### ***Results***

The plasma lidocaine concentration levels for all subjects were below LOQ (< 5 ng/mL) for all timepoints. No clinically significant skin effects were reported. Overall, the highest Draize score observed was Grade 2 erythema. Most cases resolved entirely by the 24-hour evaluation. No adverse events were reported.

### ***Summary and Conclusion***

Results of this study indicate that measurable systemic lidocaine absorption is not observed after single or repeated exposure to the Northstar Iontophoretic Lidocaine Drug Delivery System, nor is exposure associated with adverse effects or increased clinically significant dermal reactions.

## **Phase I Study: A Pharmacokinetic Study to Determine Plasma Concentrations of Lidocaine Following Application of the Northstar Iontophoretic Patch in Pediatric Subjects (BDTS-00-10) (P.I.:**

### ***Design, Objective, and Number of Subjects***

This was an open-label, randomized, repeat-application, single-center study of the Northstar system (MIP III, a TBM formulation). The objective of this study was to determine plasma concentrations of lidocaine following single and repeat treatment with the Northstar System in pediatric subjects. A total of 12 subjects who were between 6 and 15 years of age were enrolled.

<b>Variable</b>	<b>Number (%), n=15</b>
Gender:	
Male	8 (66.7%)
Female	4 (33.3%)
Age groups (years):	
5-7	4 (33%)
8-11	3 (25%)
12-15	5 (42%)
Mean	11
Range	6-15
Race:	
Caucasian	10 (83.3%)
Black	2 (16.7%)

### ***Methodology***

Subjects were randomly assigned to receive an application of the Northstar system (100 mg of lidocaine HCl and 1.05 mg of epinephrine) administered over 10 minutes at 3 of 4 application sites: upper chest, upper back, dorsum of the hand, and antecubital fossa. The second application was administered 3 hours after the first application and 30 minutes before the third application. Blood samples were collected before treatment, and at 15, 30, 60, 120, 175, 205, 225, 240, 270, 400, and 580 minutes following treatment, where  $t = 0$  is the time of first application/activation of the Northstar system, and analyzed for plasma levels of lidocaine. Plasma lidocaine concentrations were measured by the central lab using a validated LC/MS analytical method (LOQ was 5 ng/mL) and analyzed for pharmacokinetic effects. Each subject was evaluated for blanching, erythema, and edema using the Draize scale immediately following treatment and at 24 □4 hours following treatment. All subjects were monitored for adverse events.

### ***Statistical Method***

ANOVA was used as the primary analysis after the single and repeat applications. Standard noncompartmental pharmacokinetic analyses were performed on the 12 blood samples for each subject. It was expected that no lidocaine would be detected after 1 hour post-treatment, and that only very minute amounts near the limit of detection (5 ng or less) would be found between time 0 and 1 hour. If lidocaine was detected only up to 1 hour post-treatment, then 95% confidence intervals would have been constructed for mean plasma lidocaine at each time point for which lidocaine was detected. A p-value of less than 0.05 is considered statistically significant

### ***Results***

The majority of reported results of plasma lidocaine were below the minimum level of quantitation (5 ng/mL) except for two events: (1) at Baseline, Subject 009's sample was measured as "<10" (insufficient volume of sample), (2) at T225, Subject 007's sample was measured as — (ng/mL). Blanching results: completeness of blanching (under the anode) was observed at T= 15, T=205 and T=225 (after each patch was removed). After the first patch application, 92% of subjects experienced 100% blanching, after the second patch, 75% of subjects experienced 100% blanching and after the final patch, 75% of subjects were observed to have 100% blanching. The highest Draize scores were

scores of 1 (on a scale of 0 – 4). Data from a total of 72 evaluations suggested that dermal effects were very minor.

### ***Summary and Conclusion***

Results of this study indicate that active iontophoresis of lidocaine with the Northstar system, when applied at 3 different skin sites (the second Northstar system was applied 3 hours after the first and 30 minutes before the third) is not associated with increased clinically significant dermal or pharmacokinetic effects or increased observation of adverse effects overall.

### **A Pharmacokinetic Study to Determine Plasma Concentrations of Lidocaine Following Application of the Northstar Market Image II Iontophoretic Patch (98NS-01-08) (MIP II – a non-TBM formulation)**

#### ***Design, Objective, and Number of Subjects***

This was a randomized, crossover, single-center, pharmacokinetic study. The initial objective of this study was to establish that the plasma concentrations of lidocaine measured following a standard iontophoresis episode were below the concentrations required to achieve systemic therapeutic or adverse side effects (i.e., < 1 mcg/mL). A total of 13 subjects (men and women) between 19 and 44 years of age were treated with the active patch. Subsequent to the analysis of the data, a second part of the study (Protocol Amendment 2) was performed to support an absence of systemic absorption of lidocaine delivered iontophoretically (see initial part of the study). The objective was to demonstrate that detectable levels of lidocaine were found in blood samples drawn from the patch application site, and no detectable levels were found in blood samples drawn from a site distal from the patch application (antecubital area). Three subjects entered the second part of the study.

#### ***Methodology***

In the initial part of the study subjects were randomly assigned to each of the two dosing sequences. After completing the initial screening on Visit 1, eligible subjects who met inclusion/exclusion criteria returned to the clinic for skin impedance testing at Visit 2. The study patch was administered at Visit 3 per the randomization code with half the volunteers receiving the first treatment on the left hand and the remaining volunteers receiving the first treatment on the right hand. The second treatment was done on the "other" hand. The first patch was applied at 0 hour. The second patch was applied at 0.5 hour. A total of 13 subjects received 2 treatments, 1 on each hand, with lidocaine 10% and epinephrine 0.1% administered at  $3.4 \text{ m}^2 \cdot \text{min}/\text{cm}^2$ .

Blood samples were drawn for measurement of lidocaine levels from an antecubital, forearm, or hand vein at -15 min (baseline), 25 min, 55 min, 1.5 h, 2 h, 3 h, and 6 h. Subjects were discharged after the 6-hour blood sample. Dermal effects were assessed on the day of treatment and at 24 hours after treatment (Visit 4). Erythema and edema were evaluated using the Draize scale (0 to 4). Adverse events were assessed during the entire study.

In the second part of the study, the three subjects were randomized to receive two single-dose treatments (one on each hand), administered for 10 min with a total current of 17 mA•min, with the MIP-II patch on the dorsum of the hand. The first patch was applied at 0 hour (h) on one hand and the second patch was applied at 0.5 h on the "other hand." Blood samples were drawn from the antecubital area and the dorsum of the hand (directly under the anode contact area) 55 min, 1.5 h, 2 h, and 3 h after the first patch application.

Subjects were discharged after the 3-h blood sample and returned for outpatient dermal assessment at 24-h post-dose. Safety evaluation included monitoring of adverse events, an electrocardiogram (ECG) taken 1-3 h post-dose, and clinical laboratory parameters (clinical chemistry and hematology) obtained at the end of confinement. Plasma from blood samples was analyzed using a fluorescence polarization immunoassay with a limit of quantitation of 0.16 mcg/mL (initial part) and 0.2 mcg/mL (second part).

### **Results**

All concentrations of lidocaine obtained during the initial part of the study were below the limit of quantitation (LOQ) with the exception of four samples.

The 3-hour concentration of lidocaine for Subject #006 was reported as  $\sim$  mcg/mL. This result can be explained by the fact that due to poor venous access in the antecubital area, this sample was obtained from the back of the hand.

For Subject #010, the 0.92 (55 minute)-hour sample was reported as  $\sim$  mcg/mL; the 1.5-hour sample was reported as  $\sim$  mcg/mL, and the 3-hour sample was reported as  $\sim$  mcg/mL.

The concentrations of lidocaine for all other times for Subjects 006 and 010 were below the LOQ. These samples were obtained in the same area as where the lidocaine-containing patches were placed (on the back of the hand) and thus became contaminated during blood sampling.

All of the other 11 subjects had blood samples drawn per protocol in the antecubital area of the arm and none of the samples from these subjects showed concentrations above the LOQ of the lidocaine assay.

In the second part of the study, all three subjects were evaluated. All lidocaine plasma concentrations in blood drawn from the antecubital area were reported as below the limit of quantitation (LOQ) of 0.2 mcg/mL. Samples obtained from the dorsum of the hand in the same area as placement of the lidocaine-containing patches showed the following lidocaine levels: the 3-hour concentration of lidocaine for Subject 014 was  $\sim$  mcg/mL; the concentration of lidocaine for Subject 016 was  $\sim$  mcg/mL at 0.92 h,  $\sim$  mcg/mL at 1.5 h,  $\sim$  mcg/mL at 2 h, and  $\sim$  mcg/mL at 3 h.

No serious adverse events were noted during the study. Eight adverse events were recorded during the study (5/13 subjects in the initial part and 3/3 subjects in the second

part). All of the adverse events were judged as mild and included 2 incidences of burns to the hand that occurred during skin impedance testing prior to treatment and 6 incidences of purpura to the antecubital resulting from venipuncture on subjects with poor venous access. All adverse events were resolved. There were no clinically significant changes to ECG measured 1-3 h post-dose. No clinically significant laboratory abnormalities were observed

### ***Summary and Conclusions***

The objective of this protocol was to establish that plasma concentrations of lidocaine, following a standard iontophoresis treatment placed on the back of both hands, were below the concentrations required to achieve systemic therapeutic or adverse side effects (i.e., <1 mcg/mL).

In samples where lidocaine concentrations were detected, it was determined that these detectable levels were probably a direct result of the improper collection of blood samples. The blood samples should have been drawn only from the antecubital vein (as per protocol), but the samples in question were obtained from the dorsum of the hand (the area where the Northstar patch had been directly applied).

In the second portion of the study, blood samples were drawn from both the antecubital area and dorsum of the hand. Lidocaine concentration levels were detected in the blood samples obtained from the dorsum of the hand only and not from the antecubital area. No systemic absorption of lidocaine was observed in either leg of the study. Regarding safety and tolerability, the treatments were well tolerated in both the initial and second portions of the study.

### **A Blinded Crossover Pharmacokinetic and Safety Study to Assess the Plasma Concentrations and Safety Profile of Epinephrine Following Use of the Northstar Iontophoretic Lidocaine Drug Delivery System in Adolescent and Adult Subjects (Vyteris-01-01)**

#### ***Design, Objective, and Number of Subjects***

This was a double-blind, randomized, crossover, single-center, pharmacokinetic and safety study. The objective was to determine plasma concentrations of epinephrine and assess vital signs and ECGs following treatment with the Northstar System (MIP III, a TBM formulation) and a Lidocaine Alone patch (this is exactly the same as MIP but without epinephrine). A total of 29 subjects between the ages of 17-61 years of age (9 males and 20 females) were treated with both treatments at a single visit. The drugs were delivered with a total charge of 17mA.min (3.4 mA.min/cm<sup>2</sup> x 5 cm<sup>2</sup>) over a 10-minute interval.

Characteristic	Number (%) of Subjects
	Total (N = 29)
Gender	29 (100.0)
Male	9 (31.0)
Female	20 (69.0)
Age (Years)	
Mean	36.9
Standard Deviation	13.08
Median	40.0
Range	17 - 61
Race	
Caucasian	14 (48.3)
Black/African American	3 (10.3)
Hispanic	11 (37.9)
Asian	1 (3.4)
Height (cm)	
Mean	167.9
Standard Deviation	11.04
Median	165.0
Range	144.0 - 193.0
Weight (kg)	
Mean	70.2
Standard Deviation	13.90
Median	70.0
Range	48.0 - 97.0

### ***Methodology***

One Northstar System treatment and one Lidocaine Alone patch were applied to the dorsum of the hand and the antecubital fossa in an order determined by the randomization schedule. Both treatments were applied to the arm opposite to the arm that had in place an IV access device for collection of blood samples. Blood was drawn at 30 and 15 minutes prior to each treatment, at the end of the full 10 minutes treatment prior to removal of the patch, and 30 and 60 minutes after the start of treatment. Plasma epinephrine concentrations were measured using a HPLC analytical method with a limit of detection of 10 pg/mL. Lidocaine concentrations were not measured in this study. Vital signs and ECG tracings were obtained at similar timepoints as for blood collection.

The distribution of epinephrine levels categorized as <10 pg/mL (below the level of detection of the assay), 10 pg/mL to 50 pg/mL (within the normal clinical range), and >50 pg/mL (above the normal range) was summarized at each time point. The maximal changes in epinephrine levels from pre-treatment (-15 minutes) were summarized as increase, no change, and decrease.

Shift tables were also used to display the number of subjects with epinephrine values shifting from baseline to the maximal post-treatment values for three categories: <10 pg/mL, 10 pg/mL to 50 pg/mL, and >50 pg/mL. Since most of the epinephrine levels recorded over time were <10 pg/mL (below the level of detection of the assay), no descriptive statistics (mean, standard deviation, median, and range) were used as had been originally planned.

**The normal clinical range for plasma epinephrine levels is 5 pg/mL to 50 pg/mL.** Within 1 hour after treatment with the Northstar or Lidocaine Alone system, any increase in a subject's epinephrine level to a value greater than 50 pg/mL or more than two standard deviations above the pre-treatment mean would have been considered "clinically important."

Epinephrine is naturally occurring at variable systemic concentrations, often below assay sensitivity levels, so this parameter was not likely to be amenable to traditional pharmacokinetic modeling. It was expected that a number of subjects would have epinephrine levels below the sensitivity of the assay. In those instances, the lower limit of detection was imputed for use in the computation of summary statistics.

## Results

### Pharmacokinetic:

**Table 5. Plasma Epinephrine Concentration Level by Time Point**

Time Point	Number (%) of Subjects Epinephrine Level (pg/mL)	
	Northstar (N = 29)	Lidocaine Alone (N = 29)
-30 minutes		
<10 pg/mL	18 (62.1)	20 (69.0)
10 - 50 pg/mL	11 (37.9)	9 (31.0)
>50 pg/mL	0	0
-15 minutes		
<10 pg/mL	21 (72.4)	24 (82.8)
10 - 50 pg/mL	8 (27.6)	5 (17.2)
>50 pg/mL	0	0
10 minutes		
<10 pg/mL	18 (62.1)	22 (75.9)
10 - 50 pg/mL	10 (34.5)	7 (24.1)
>50 pg/mL	0	0
Missing	1 (3.4)	0
30 minutes		
<10 pg/mL	15 (51.7)	22 (75.9)
10 - 50 pg/mL	14 (48.3)	7 (24.1)
>50 pg/mL	0	0
60 minutes		
<10 pg/mL <sup>1</sup>	17 (58.6)	19 (65.5)
10 - 50 pg/mL	12 (41.4)	10 (34.5)
>50 pg/mL	0	0

As noted by above table, there is endogenous epinephrine present in Lidocaine Alone arm.

With both treatments no subjects had an epinephrine concentration above 50 pg/mL (normal range, 5-50 pg/mL). Plasma epinephrine concentrations in the range of 10-50 pg/mL at the end of treatment (10 minutes), compared with 15 minutes pre-treatment, were observed, respectively, in 34.5 and 27.6% of the Northstar treated group and in 24.1 and 17.2% of the Lidocaine Alone treated group (Table 10). In an examination of the maximum change from pre-treatment levels, fifteen (51.7%) subjects versus 11 (37.9%) subjects had increases, 11 (37.9%) subjects versus 17 (58.6%) subjects had no changes, and 3 (10.3%) subjects versus 1 (3.4%) subject had decreases after treatment with the Northstar and Lidocaine Alone systems, respectively (Table 11).

Shift values of epinephrine levels for samples collected 15 minutes prior to treatment were compared with maximal values after treatment. There were no notable differences in the shift values for epinephrine levels following treatment with either the Northstar system or Lidocaine Alone system. After treatment with the Northstar and Lidocaine Alone systems, respectively, 19 (65.5%) subjects versus 20 (69.0%) subjects had no shift

in epinephrine values; and 0 subjects versus 1 (3.4%) subject shifted from the 10 pg/mL to 50 pg/mL group to the <10 pg/mL group. After treatment with the Northstar and Lidocaine Alone systems, respectively, there were 10 (34.5%) subjects versus 8 (27.6%) subjects who shifted from the <10 pg/mL group pretreatment to the 10 pg/mL to 50 pg/mL group (Table 12).

**Safety:**

Most subjects had no or only very slight (Draize score = 0 to 1) erythema (79%) and edema (93%) immediately after treatment. After 24 hours, 81% and 100% of subjects had no erythema and no edema, respectively. Draize scores for erythema and edema were comparable for both the Northstar and Lidocaine Alone systems. The number of subjects who experienced at least one treatment-emergent AE was low: 6 (20.7%) versus 3 (10.4%) subjects after treatment with the Northstar and Lidocaine Alone systems, respectively. Adverse events were generally mild or moderate in intensity with severe AEs occurring in only one subject after treatment with the Northstar system. No subjects experienced serious adverse events (SAEs) in this study, and there were no adverse events that led to discontinuation from the study. There were no clinically important treatment-related changes in vital signs observed after the application of either the Northstar system (containing epinephrine) or the Lidocaine Alone system. However, one patient with abnormal transaminases (aspartate transaminase [AST] = 65 U/L and alanine transaminase [ALT] = 53 U/L) at baseline did develop a transient SIQ3T3 pattern that initially appeared 60 minutes after treatment with the Northstar system. This abnormality resolved spontaneously approximately 2 hours later, just prior to treatment with the Lidocaine Alone system. There were no adverse effects, changes in vital signs, or ECG abnormalities that were considered to be caused by the epinephrine in the Northstar system.

**Conclusions**

There were no subjects who had epinephrine levels that were >50 pg/mL (above the normal range) during the course of the study.

Also, there were no notable differences in the maximal changes from the pre-treatment values of epinephrine between the Northstar and Lidocaine Alone systems.

Neither the Northstar system nor the Lidocaine Alone system caused clinically important changes in the epinephrine levels of subjects.

No changes in systemic levels of epinephrine were detected in any subject after treatment with either patch system, and no epinephrine-related effects were observed during the study.

Both patch systems were safe and well tolerated. There were no adverse effects, changes in vital signs, or ECG abnormalities that were considered to be caused by the epinephrine in the Northstar system.

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

/s/

-----  
David Lee  
6/30/03 12:18:31 PM  
BIOPHARMACEUTICS

Suresh Doddapaneni  
6/30/03 12:39:39 PM  
BIOPHARMACEUTICS