

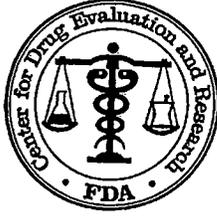
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-504

STATISTICAL REVIEW(S)

Cycle 2



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIostatISTICS

Statistical Review and Evaluation

STABILITY STUDIES

NDA: 21-504/N-000-BZ

Name of drug: Northstar lidocaine iontophoretic drug delivery system

Indication: local dermal anesthesia

Applicant: Vyteris

Dates: letter 18 March 2004

Review priority: resubmission

Biometrics division: Division of Biometrics II

Statistical reviewer: Thomas Permutt (team leader)

Concurring reviewer: Karl Lin, Ph.D.

Medical division: Anesthetic, Critical Care and Addiction Drug Products
(HFD-170)

Chemistry reviewer: Ravi Harapanhalli, Ph.D.

Project manager: Kimberly Compton

Keywords: NDA review, stability studies

NDA 21-504 was found to be approvable 25 July 2003. As part of their response the applicant has submitted updated stability data on three batches for 24 months. The requested expiration dating is also for 24 months.

All the tested characteristics remained within specifications throughout the 24 months. No statistical extrapolation is required. The submission nevertheless includes statistical analysis consistent with current guidance. According to this analysis the shelf life would be limited by two parameters (Container Closure — and Cathode Reservoir: Preservative Assay) to — . Other parameters would all be predicted to remain within specifications with 95 percent confidence for longer periods.

The requested expiration dating for 24 months appears to be well supported.

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

/s/

Thomas Permutt
4/19/04 01:51:23 PM
BIOMETRICS

Karl Lin
4/19/04 01:56:13 PM
BIOMETRICS
Concur with review



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-504
Name of drug: Northstar Lidocaine Iontophoretic Drug delivery System
(Northstar System)
Applicant: Vyteris, Inc
Indication: Local Dermal Anesthesia on Intact Skin
Documents reviewed: Electronic Submission
 \\CDSESUB1\N21504\N_000\2002-09-25\clinstat
Project manager: Kimberly Compton
Clinical reviewer: Arthur Simone, M.D.
Dates: Received 09/25/2002; user fee (10 months) July 24, 2003
Statistical reviewer: Mushfiqur Rashid, Ph.D.
Statistics team leader: Thomas Permutt, Ph. D.
Biometrics division director: S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, ANOVA, ordinal logistic
regression

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The applicant has proposed Northstar system (Northstar Lidocaine Iontophoretic Drug delivery System) for ————— The applicant claimed that both adult subjects (study BDTS-99-67) and children ages 5 to 17 years (study BDTS-99-68) treated with the Northstar system reported significantly less pain associated with venipuncture or IV cannulation compared with the subject with the placebo system. In study BDTS-99-67, scores measured with a 10 cm Visual Analogue Scale (VAS) indicated that adult subjects treated with the Northstar system reported significantly less pain associated with the venipuncture or IV Cannulation compared with subjects treated with placebo system. The Nine-face Interval scale (NFIS) scores indicated that pediatric subjects (ages between 5 to 17 years) subjects treated with the Northstar System reported significantly less pain associated with venipuncture or IV cannulation compared with subjects treated with placebo system. The evidence from these two studies reviewed indicates support for the efficacy and safety of the Northstar system —————

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Background:

Vyteris, Inc. is developing an iontophoretic drug delivery system, called the Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar), to non-invasively provide ————— Iontophoretic drug delivery is the migration of drug ions through the skin in response to the establishment of an elected potential. By passing a weak electrical current through a suitably designed transdermal drug delivery patch, a drug ion of a particular charge contained in a specially designed reservoir may be driven out of the reservoir and to intact skin. The safety of the iontophoretic process in humans has been established through a history of commercial application that spans over two decades.

The drugs in Northstar system are lidocaine hydrochloride monohydrate (lidocaine HCl) 10%, an anesthetic and epinephrine bitartrate (epinephrine) 0.1%, a vasoconstrictor, added to lengthen the duration of the anesthetic response produced by lidocaine. The applicant has mentioned that until now the Northstar system has no approved indications in the United States (US); however, the efficacy of the iontophoretic process in humans has been established through a history of commercial applications that spans over two decades. The applicant has also mentioned that both lidocaine HCl and epinephrine are established drugs with well characterized and well tolerated response profiles.

In this submission, the applicant has investigated the safety and efficacy of Northstar system for the indication of _____ based on two protocols BDTS-99-67 and BDTS-99-68.

Previous studies with the Northstar system indicated that 10% lidocaine in combination with 0.1% epinephrine, delivered with a total charge of 17mA•min (3.4mA•min/cm²) over a 10-minute interval, provided the optimal dose. Thus, these studies compared the Northstar system, administering 10% lidocaine and 0.1% epinephrine, with an otherwise identical placebo system in which lidocaine replaced with NaCl.

Study Design:

In study BDTS-99-67, there were 270 efficacy evaluable adult subjects. The primary objective of this randomized, double blind, parallel group, placebo controlled, prospective, multicenter study was to demonstrate the safety and efficacy of the Northstar system compared with placebo when used for _____ on adults.

In study BDTS-99-68, there were 256 efficacy evaluable pediatric subjects. The primary objective of this randomized, double blind, parallel group, placebo-controlled, prospective, multicenter study was to demonstrate the safety and efficacy of the Northstar system with placebo system when used for _____ in children 5 to 17 years of age.

Statistical Analyses:

Study BDTS-99-67:

The primary assessment of efficacy (dermal anesthesia) was the 10-cm visual analogue scale (VAS) score determined by the subject immediately after venipuncture/IV cannulation. The applicant analyzed the results from the primary efficacy variable using analysis of variance model: $VAS\ score = Center + Procedure + Treatment + Error$.

Study BDTS-99-68:

The primary assessment of efficacy (dermal anesthesia) was the nine face interval score (NFIS) assessment completed by the subject immediately after venipuncture/IV cannulation. The NFIS score was assessed by the parent(S)/guardian (S) for the 2 younger age groups (5 to 7 and 8 to 11 years). The applicant analyzed the results for the primary efficacy variable using the ordinal logistic regression model: $NFIS = Center + Procedure + Age\ group + Treatment + Error$.

Applicant's Results and Conclusions:

Study BDTS-99-67:

The applicant reported that subjects treated with the Northstar system experienced significantly less pain from the venipuncture /IV cannulation procedures than did subjects treated with the placebo system. Furthermore, a greater number of subjects treated with Northstar system reported feeling little or no pain in contrast to subjects treated with the placebo system.

Study BDTS-99-68:

The applicant reported that NFIS, weighted NFIS, and VAS scores indicated that children ages 5 to 17 years treated with the Northstar system experienced significantly less pain from the venipuncture/IV cannulation procedures than did subjects treated with the placebo system. There were no notable differences among the three age groups.

1.3 PRINCIPAL FINDINGS

The primary objectives of these studies were to demonstrate the safety and efficacy of the Northstar system compares with the placebo system

— ne results demonstrated that both adult subjects and children ages 5 to 17 years treated with the Northstar system reported significantly less pain associated with venipuncture of IV cannulation compared with subjects treated with placebo system. There were no notable differences in the pain upon venipuncture or IV cannulation among the different age categories in the pediatric subjects treated with the Northstar system.

Subgroup analyses of the primary endpoints in both studies (in all subgroups analyzed) indicated that subjects receiving treatment with the Northstar system reported feeling less pain immediately after the procedure than subjects receiving treatment with placebo.

There were no statistically significant differences between the two treatment groups for the incidence of any specific treatment related adverse events

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Since 1995, Vysteris, Inc. (formerly Drug Delivery Technologies, Inc., and prior to that Becton Dickinson transdermal Systems, Inc. [BDTS]), has evaluated the Northstar system 2618 times in more than 2079 subjects in 24 clinical studies conducted under IND No. 48,365. The applicant mentioned that seventeen of these studies evaluated the efficacy of the Northstar system in providing localized dermal anesthesia in a non-invasive manner, by the delivery of lidocaine HCl in combination with a vasoconstrictor, epinephrine. Iontophoretic drug delivery is the migration of drug ions through the skin in response to the establishment of an electrical potential. By passing a weak electrical current through a suitably designed transdermal drug delivery patch, a drug ion of a particular charge contained in a specially designed reservoir may be driven out of the reservoir and into intact skin. In this submission, the applicant has investigated the safety and efficacy of Northstar system for skin based on two protocols BDTS-99-67 and BDTS-99-68.

The drugs in Northstar system are lidocaine hydrochloride monohydrate (lidocaine HCl) 10%, an anesthetic and epinephrine bitartrate (epinephrine) 0.1%, a vasoconstrictor, added to lengthen the duration of the anesthetic response produced by lidocaine. The applicant has mentioned that until now the Northstar system has no approved indications in the United States (US); however, the efficacy of the iontophoretic process in humans has been established through a history of commercial applications that spans over two decades. The applicant has also mentioned that both lidocaine HCl and epinephrine are established drugs with well characterized and well tolerated response profiles.

On September 25, 2002, the applicant submitted NDA 20504 for Northstar System. In this submission, the applicant has investigated the safety and efficacy of Northstar system for the indication of based on two protocols BDTS-99-67 and BDTS-99-68.

2.2 DATA ANALYZED AND SOURCES

The applicant provided two studies (BDTS-99-67 and BDTS-99-68) to demonstrate the safety and efficacy of Northstar system for the indication of

Additionally, six controlled studies were submitted to further profile the Northstar system and to broaden the types of procedures for which the Northstar system would be indicated: 98NS-01-09, 98NS-01-11, 98NS-01-10, BDTS-99-25, BDTS-99-24, and BDTS-00-16. These supportive studies investigated blanching and the depth of dermal anesthesia achieved with the Northstar system. They also provided data for the the laser treatment of superficial skin lesions. A total of 258 subjects were evaluated for efficacy in these studies, providing supportive data for the NDA. Table 1 describes these studies briefly.

Table 1: Table of Studies

Study Number Number of centers (n)	Study design	Treatment arms	Primary measures of efficacy
98NS-01-09 Single center	Phase I, double-blind, randomized, placebo and active controlled, parallel group, and cross-over	Northstar Placebo	Degree of —
98NS-01-11 Single center	Phase I, double-blind, randomized, placebo controlled, and parallel group	Northstar Placebo	Degree of —
98NS-01-10 Single center	Phase II, double-blind, randomized, placebo controlled, and parallel group study in children	Northstar Placebo	NFIS and/or VAS scores
BDTS-99-25 Single center	Phase I, single - blind, randomized, placebo controlled, and parallel group	Northstar Placebo	Degree of —
BDTS-99-24 Single center	Phase I, single - blind, randomized, placebo controlled, and parallel group	Northstar Placebo	Depth of to which sensation is eliminated after treatment
BDTS-00-16 Multicenter	Phase III, double-blind, randomized, placebo controlled, and parallel group	Northstar Placebo	— pain assessment scores

The studies varied from the two trials in that they were conducted earlier in the trial process, used different designs, different phases (phase I and phase II) and dosage strengths, and /or defined the primary efficacy variable differently. Due to these variations, this reviewer primarily focused his review on studies BDTS-99-67 and BDTS-99-68. The reviewed documents were electronic and the data from these studies were archived in the FDA internal electronic document room under network path \CDSESUB1\N21504\N_000\2002-09-25.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

The designs of two studies BDTS-99-67 and BDTS-99-68 were similar with differences in the sample sizes, primary endpoints, and patient populations. There were 270 adult patients in BDTS-99-67 study whereas there were 256 child patients in BDTS-99-68. Scores measured in 10-cm Visual analogue Scale (VAS) in BDTS-99-67 study whereas both nine face interval scale and/VAS scores (in 10 cm) were measured in BDTS-99-68.

Both studies compared the performance of the Northstar system (administering lidocaine 10% and epinephrine 0.15) with placebo (an iontophoretic drug delivery system administering saline and epinephrine 0.1%) and evaluated the — in preparation of venipuncture or IV cannulation.

2.3.1 APPLICANT'S RESULTS AND CONCLUSIONS

The results demonstrated that both adult subjects and children ages 5 to 17 years treated with the Northstar system reported significantly less pain associated with the venipuncture or IV cannulation compared with subjects with the placebo system. There were no notable differences in the pain upon venipuncture or IV cannulation among the different age categories in the pediatric subjects treated with the Northstar system.

2.3.2 STATISTICAL METHODOLOGIES

Efficacy:

In study BDTS-99-67, the primary measure of efficacy was the VAS scores. The VAS scores are within 10 cm determined by the subject immediately after venipuncture/IV cannulation. In study BDTS-99-68, the primary measure of efficacy was NFIS scores. The NFIS scores were assessed by the parent(s) or guardian(s) for the 2 younger age groups (5 to 7 and 8 to 11 years). The NFIS assessment was completed by the subject immediately after venipuncture/IV cannulation.

The efficacy endpoint (VAS scores) in BDTS-99-67 was analyzed via analysis of variance model with treatment group, center and procedure as main effects. However, the efficacy endpoint in BDTS-99-88 was analyzed using the ordinal logistic regression with main effects as center, procedure, age-group, and treatment.

Safety:

BDTS-99-67

The safety of Northstar system was assessed using an analysis of Draize scores for both edema and erythema. The Cochran-Mantel-Haenszel mean score test, stratified by center and procedure, was used to test for treatment differences in the Draize scores between the Northstar and placebo groups. The ordinal logistic regression analysis that was also originally planned in the protocol could not be performed because of the sparse distribution of Draize scores.

Adverse events were tabulated by treatment group using the Medical Dictionary for Drug Regulatory Affairs (MedDra) coding terms sorted by body system. The incidence of AEs in each treatment group was also summarized by seriousness, intensity, and relationship to study drug. Vital sign measurements were summarized using descriptive statistics.

BDTS-99-68

The Draize scores were analyzed using a Cochran-mantel-Haenszel mean scores test, stratified by center, procedure, age group, and treatment group, to determine the treatment difference. Incidence of adverse events (coding terms [MeDRA] sorted by body system) was summarized by treatment group, intensity, and relationship to the study medication. Vital sign measurements were summarized using descriptive statistics.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.3.1 Statistical Review and Evaluation of Evidence of BDTS-99-67

Study BDTS-99-67 was a randomized, double-blind, placebo controlled, prospective, multicenter (5 centers) study conducted by five investigators. There were 276 subjects enrolled in the study (137 Northstar system; 139 placebo system). Of the 276 subjects enrolled in the study, 270 subjects (98%; 134 in Northstar system, 136 placebo system) were evaluated for efficacy. A total of 270 (98%) subjects completed the study.

Sample Size Estimation:

A sample size of 125 subjects per group was planned to yield at least 90% power to detect a difference in VAS score of about 0.9 score units between groups using a 2-sided test at the 5% significance level, assuming a common standard deviation of 2.2 units. The sponsor mentioned that 275 subjects were planned to enroll at approximately 6 investigative sites to achieve at least 250 evaluable subjects. Roughly equal number of subjects were expected to be enrolled at each site with no more than 60 subjects at any site. Roughly equal numbers of each procedure (venipuncture or IV cannulation) were expected to be performed at each site, and neither procedure was to comprise <40% of the enrollment for that investigating site.

Efficacy Assessments:

The primary assessment of efficacy () was the 10-cm VAS score determined by the subject immediately after venipuncture/IV cannulation.

Safety:

Safety was assessed by analyzing Draize scores, by monitoring AEs and by measuring vital signs.

Randomization:

Subjects who qualified for the study at baseline were randomized to receive treatment with either the Northstar or placebo system 1:1 ratio according to a computer-generated randomization schedule. Subjects were assigned randomization numbers in chronological order with each procedure group (venipuncture or IV cannulation) as they became eligible for the study. Randomization was stratified by procedure group within investigative sites.

Demographic and Baseline Characteristics:

A summary of the demographic and baseline characteristics of all randomized subjects is presented in the following Table A.1 in the appendix. The majority of subjects were female (65%) and Caucasian (75%). In addition, the majority of subjects were less than 65 years of age (86%). A total of 140 subjects (51%) were randomized to receive a venipuncture and 136 subjects (49%) were randomized to receive IV cannulation. Both treatment groups were similar with respect to medical history, concomitant conditions, and previous and concomitant medication use.

Efficacy Analyses:

The applicant's summary of mean VAS scores are presented in Table 2.

Table 2: Mean Pain Assessment Immediately Post Procedure Based on Visual Analogue Scale (VAS Scores) in Study BDTS-99-67

VAS Scores	Number (%) of Subjects	
	Northstar (N=134)	Placebo (N=136)
0 - 1	1 (83)	44 (32)
>1 - 2	8 (9)	33 (24)
>2 - 3	4 (3)	15 (11)
>3 - 4	2 (2)	10(7)
>4 - 5	5 (4)	11 (8)
>5 - 6	2 (2)	7 (5)
>6 - 7	0	11 (8)
>7 - 8	2 (2)	3 (2)
>8 - 9	0	0
>9 - 10	0	2 (2)
Mean ¹ (sd)	0.77 (1)	2.53 (2)

¹The p-value was <0.001 based on the analysis of variance (ANOVA) model: VAS score =Center + Procedure + Treatment + Error. VAS= Visual analogue scale (0-10 cm) : smaller scores indicate less pain. SD= Standard deviation.

The VAS scores were significantly lower in the Northstar system group than in the placebo group (Mean VAS score \pm s.d.: 77 ± 1.486 and 2.53 ± 2.295 , respectively; p-value <0.001) indicating that subjects treated with the Northstar system reported feeling significantly less pain than did subjects treated with placebo system. The applicant concluded that considerably more subjects in the Northstar system group reported little or no pain (VAS score of 0 or 1) compared with subjects in the placebo group (111 subjects [82.8%] and 44 subjects [32.4%], respectively). Consequently, fewer subjects in the Northstar system group than in the placebo group experienced pain that was evaluated as being more severe; VAS scores of greater than 3 were observed in only 11 (8.2%) subjects treated with the Northstar system compared with 44 (32.4%) subjects treated with the placebo system.

Subgroup Analyses:

This reviewer conducted analyses of the primary outcome by gender, age, race and site. These sub-group analyses results are summarized below.

Gender

This reviewer conducted treatment by the gender interaction test using the ANOVA model with site, procedure, treatment group, gender and gender x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.1262) between gender and the treatment-group. The following table summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population.

Table 3: Mean Pain Assessment Immediately Post Procedure Based on Visual Analogue Scale (VAS) by Age:

VAS	Placebo (n=136)		Active (N=134)	
	Male	Female	Male	Female
N	50	86	42	92
Mean	1.93	2.87	0.756	0.77

The subgroup analysis of VAS scores by gender showed that, in either sex, subjects receiving treatment with the Northstar system reported feeling less pain immediately after the procedure than subjects receiving treatment with placebo.

Race:

This reviewer conducted treatment by the race interaction test using the ANOVA model with site, procedure, treatment group, race and race x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.3691) between race and the treatment-group. The following table summarizes the event rates in the two treatment groups by gender for the primary efficacy patient population.

Table 4: Mean Pain Assessment Immediately Post Procedure Based on Visual Analogue Scale (VAS) by Race:

VAS	Placebo (n=136)		Active (N=134)	
	Caucasian	Other	Caucasian	Other
N	102	34	98	36
Mean	2.39	2.92	0.70	0.95

The subgroup analysis of VAS scores by race (Caucasian and non-Caucasians) showed that in both categories subjects receiving treatment with the Northstar system reported less pain immediately after the procedure than subjects receiving treatment with placebo.

Age Group

This reviewer conducted treatment by the race interaction test using the ANOVA model site, procedure, treatment group, race and age-group x treatment-group as fixed effects. The test failed to detect that the interaction (p-value 0.2698) between race and the treatment-group. The following table summarizes the event rates in the two treatment groups by age-group for the primary efficacy patient population.

Table 5: Mean Pain Assessment Immediately Post procedure Based on Visual Analogue Scale (VAS) by Age :

VAS	Placebo (n=136)		Active (N=134)	
	Age <65	Age ≥65	Age <65	Age ≥65
N	117	19	117	17
Mean	2.62	1.92	0.75	0.94

The subgroup analysis of VAS scores by age (<65 years and ≥65 years) showed that in both age categories subjects receiving treatment with the Northstar system reported less pain immediately after the procedure than subjects receiving treatment with placebo

Site:

This reviewer conducted treatment by the site interaction test using the ANOVA model with site, procedure, treatment group, race and site x treatment-group as fixed effects. The test failed to detect that the interaction (p-value 0.2983) between race and the treatment-group.

Safety

There were no statistically significant differences between the two treatment groups for the incidence of any specific treatment related adverse events. The safety results are summarized as follows.

The sponsor reported that there were no significant differences in Draize scores associated with edema between the Northstar and placebo groups. At the anode site, most of the subjects in both Northstar and placebo groups had no or very slight edema (scores of 0 or 1) within 10 minutes of patch removal (100% and 99% respectively). At the cathode site, most of subjects in both the Northstar and placebo groups also had no or very light edema within 10 minutes of patch removal (99% and 99% respectively).

Overall, there were no significant differences in Draize scores associated with erythema between Northstar and placebo groups. At the anode site, most of the subjects in both the Northstar and placebo groups had either no or very slight erythema (99% and 96%, respectively) within ten minutes of patch removal. At the cathode site, 100 (74%) of the subjects in the Northstar group and 97 (70%) of the 138 subjects in the placebo group exhibited no or very slight erythema within 10 minutes after patch removal.

The number of subjects who experienced at least 1 treatment emergent AE was low; 16 of 136 (12%) subjects in the Northstar group experienced compared with 10 of 138 (7%) subjects in the placebo group. The incidence of treatment emergent AEs considered by the investigator to be related to the study drug/device was also low between the Northstar and placebo groups: 7 out 136 (5%) subjects in the Northstar group and 4 out of 138 (3%) subjects in the placebo group experienced treatment related AEs.

No subjects experienced any serious treatment-emergent AEs in this study, and no subjects experienced treatment-emergent AEs that led to discontinuation from the study. No subjects died during this study.

No deaths, SAEs, or other significant AEs occurred in this study. Additionally, no subjects discontinued from the study due to AEs. See medical review for further safety results.

Conclusions:

The subjects treated with the Northstar system experienced significantly less pain from the venipuncture /IV cannulation procedures than did subjects treated with the placebo system. Furthermore, a greater number of subjects treated with Northstar system reported feeling little or no pain in contrast to subjects treated with the placebo system.

2.3.3.2 Statistical Review and Evaluation of Evidence of BDTS-99-68 (Local Dermal Anesthesia in children)

Introduction and Background

The primary objective of this study was to demonstrate the safety and efficacy of the Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar) compared with a placebo system — n intact skin in children aged 5 to 17 years. The secondary objective was to assess the pain experienced during removal of the patch, due to adhesive.

Study Design:

Study BDTS-99-68 was a randomized, double blind, parallel group, placebo controlled, prospective, multicenter study conducted by 7 investigators who enrolled 272 subjects (136 Northstar system; 136 placebo system). Each subject received a single treatment with either a Northstar or a placebo system, approximately 15 minutes prior to a scheduled venipuncture or IV cannulation procedure. Of the 272 subjects enrolled in the study, 256 subjects (94%; 130 Northstar system, 126 subjects in placebo system) were evaluated for efficacy. A total of 249 (92%) subjects completed the study.

Subjects evaluated the pain they experienced from the venipuncture/IV cannulation procedure using the Nine-Face Interval Scale (NFIS). The parent (s) or guardian(s) responsible for the subject recorded their perception of the pain experienced by the subject, using the same scale, to provide supportive information. In addition, the oldest age group (12 to 17 years) also assessed pain using a Visual analogue scale (VAS). Pain experienced during removal of patch, due to adhesive, was assessed by all subjects and parent(s)/guardians in the same manner using the same scales. Skin at the application site was examined for dermal reactions following removal of the patch system. Each subject was to return to the center approximately 24 (± 8) hours later so that the treatment area

could be assessed again for dermal reactions. Additional visits may have been required if dermal effects, (Draize scores ≥ 3) considered to be clinically significant by the principal investigator (PI), persisted at Visit 2. If this occurred, the subject was to be allowed until the events were resolved, or in the opinion of the PI, the event was no longer considered clinically significant.

Sample Size Estimation:

Approximately 275 subjects were planned to enroll at approximately 6 investigative sites to obtain at least 250 evaluable subjects (125 subject in each treatment group). This number would yield at least 90% power to detect a difference 0.9 VAS score units between groups, using a two-sided test at the 5 level of significance level, assuming a common standard deviation of 2.2 units.

Roughly equal number of subjects were planned to enroll at each site, with no more than 60 subjects at any site. Subjects were grouped into 3 categories by age: 5 to 7, 8 to 11, and 12 to 17 years of age. Roughly equal numbers of each procedure were expected to be performed at each site for each age group, and neither procedure was to comprise > 40% of the enrolment for that investigative site.

Demographic and Baseline Characteristics

A summary of the demographic and baseline characteristics of all enrolled subjects is presented in Table A.2 in the appendix. It appears that more than half of the subjects in both treatment groups were male (54%) and Caucasian (57%). The age of the enrolled subjects ranged from 5 to 17 years, and overall 26.5% of the subjects were in age group 1 (5 to 7 years), 36% in age groups 2 (8 to 11 years) and 38% in age group 3 (12 to 17 years). Both treatment groups were similar with respect to medical history, concomitant conditions and concomitant medication use.

Randomization

Subjects who qualified for the study at baseline were randomized to receive treatment with either the Northstar or placebo system in 1:1 ratio according to a computer-generated randomization schedule. Randomization was stratified by procedure type and age group with investigative sites. Subjects were assigned randomization numbers in chronological order within each procedure group (venipuncture or IV cannulation) as they eligible for the study

Efficacy Assessments:

The primary assessment of efficacy (dermal anesthesia) was the NFIS assessment completed by the subject (in all age-groups) immediately after venipuncture/IV cannulation. In addition to the raw NFIS (A through I), a weighted NFIS was calculated as A=0.08, B=0.22, C=0.34, D=0.47, E=0.60, F=0.78, G=0.82 and I=0.97. This reviewer could not locate any rationale for using these weights for the NFIS scores A through I in the submission. However, it is mentioned that smaller numbers indicate less pain. Pain experienced during removal of the patch, due to the adhesive, was also assessed by all subjects using the same scales.

An ordinal logistic regression model was used to compare the difference between the two treatments with regard to the NFIS score recorded both post-venipuncture/IV cannulation and immediately following patch removal.

The model used was:

NFIS = Center + Procedure + Treatment + Age + residual.

The applicant mentioned that interactions of center by treatment, procedure by treatment, and age by treatment, which were originally planned in the protocol, were excluded from the model because of sparseness of the data. However, this reviewer conducted the treatment by subgroup interaction.

Safety Assessments:

Safety was assessed by analyzing Draize scores, by monitoring adverse events, and by measuring vital signs.

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Efficacy Analyses:

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The distribution of NFIS scores assessed by the subject immediately after the procedure is presented in Table 6.

Table 6: Pain Assessment (Immediately Post-procedure) by Subject Based on Nine-face Interval Scale Scores

	Number (%) of Subjects					
	Northstar (N=130)			Placebo (N=126)		
	5-7 years	8-11 years	12-17 years	5-7 years	8-11 years	12-17 years
A(1)	10 (29)	15 (33)	12(24)	5 (18)	5 (10)	5(10)
B(2)	6 (17)	9 (20)	10 (20)	0	10 (20)	8(16)
C(3)	4 (11)	4 (9)	11(22)	2 (7)	8(16)	6 (12)
D(4)	4 (11)	5 (11)	8 (16)	3 (11)	4 (8)	6(12)
E(5)	3(9)	6 (13)	6 (12)	5 (18)	9 (18)	13 (27)
F(6)	3(9)	2(4)	3(6)	4 (14)	6 (12)	6 (12)
G(7)	2(6)	2(4)	0	3(11)	3(6)	4(8)
H(8)	1(3)	0	0	0	3(6)	1(2)
I(9)	2(6)	2(4)	0	6(21)	1(2)	0
p-value	<0.001					

Note: p-value was based on the ordinal logistic regression model; score = site, procedure, age-group, and treatment. Nine-Face Interval Scale (NFIS) Score: smaller numbers indicate less pain.

The distribution of NFIS scores indicates that subjects treated with Northstar system experienced significantly less pain from the venipuncture /IV cannulation procedures than did subjects treated with the placebo system (p-value <0.001).

In addition, there was no significant difference between the two treatment groups (p-value 0.938) in weighted NFIS scores immediately following the patch removal.

Subgroup Analyses:

This reviewer conducted analyses of the primary outcome by gender, age-group, race and site with respect to the primary endpoint. These sub-group analyses results are summarized below.

Gender

This reviewer conducted treatment by the gender interaction test using the ordinal logistic regression model with site, procedure, treatment group, gender and gender x treatment-group as fixed effects. The test failed to detect the interaction (p-value 0.1650) between gender and the treatment-group. The following table summarizes the pain assessment scores in the two treatment groups by gender for the primary efficacy variable.

Table 7: Pain Assessment Immediately Post Procedure by Subject Based on Weighted Nine Face Interval Scale Score by Gender (ITT population)

	Number (%) of Subjects			
	Northstar (N=130)		Placebo (N=126)	
	Male (N=69)	Female (N=61)	Male (N=67)	Female (N=59)
A(1)	19(28%)	18(30%)	11(16%)	4(17%)
B(2)	15(22%)	10(16%)	9(13%)	9(15%)
C(3)	10(15%)	9(15%)	7(10%)	9 (15%)
D(4)	6(9%)	11(18%)	8(12%)	5(9%)
E(5)	10(15%)	5(8%)	14(21%)	13 (22%)
F(6)	4(6%)	4(7%)	9(13%)	7(12%)
G(7)	1(1%)	3(5%)	4(6%)	6(10%)
H(8)	0(0%)	1(2%)	1(2%)	3(5%)
I(9)	4(5.8%)	0(0%)	4(6%)	3(5%)

Age Group:

This reviewer conducted treatment by the age-group interaction test using the logistic regression model with center, treatment group, age-group (5-7 years, 8-11 years, and 12-17 years) and age-group x treatment-group as fixed effects. There was no interaction (p-value 0.5551) between age and the treatment-group. The distribution of pain assessment scores by age-group were summarized in Table 6.

Race:

The following table summarizes the pain assessment scores in the two treatment groups by race for the primary efficacy variable.

Table 8: Pain Assessment Immediately Post Procedure by Subject Based on Weighted Nine Face Interval Score by Gender (ITT population)

VAS	Placebo (n=126)			Active (N=130)		
	Caucasian (N=73)	Hispanic N=(35)	Other (N=18)	Caucasian (N=76)	Hispanic (n=39)	Other (N=15)
A(1)	5(7%)	9 (26%)	1(6%)	20 (26%)	13(33%)	4 (27%)
B(2)	8 (11%)	6 (17%)	4 (22%)	13 (17%)	8 (21)	4 (27%)
C(3)	9 (12%)	5 (14%)	2 (11%)	11 (15%)	7 (18%)	1 (7%)
D(4)	7 (10%)	2 (16%)	4 (22%)	11 (15%)	5 (13%)	1 (7%)
E(5)	20 (27%)	5 (14%)	2 (11%)	12(16%)	2 (5%)	1 (7%)
F(6)	13 (18%)	2 (6%)	1 (5.6%)	3 (4%)	3 (8%)	2 (13%)
G(7)	4 (6%)	3 (9%)	3 (17)	3 (4%)	3 (8%)	2 (13%)
H(8)	2 (3%)	2 (6%)	0	0	0	0
I(9)	5 (7%)	1 (3%)	1(6%)	3 (4%)	0	1 (7%)

This reviewer conducted treatment by the race interaction test using the ordinal logistic regression model using center, procedure, treatment group, race and race x treatment - group as fixed effects. The test failed to detect the interaction (p-value 0.6299) between race and the treatment-group.

Site:

This reviewer conducted treatment by site interaction test using the ordinal logistic

regression model using site, procedure, treatment group, race and race x treatment -group as fixed effects. The test failed to detect that the interaction (p-value 0.7149) between site and the treatment-group.

Conclusions:

The efficacy result indicates that subjects treated with Northstar system experienced significantly less pain from the venipuncture /IV cannulation procedures than did subjects treated with the placebo system (p-value <0.001).

Safety Results

There were no statistically significant differences between the two treatment groups for the incidence of any specific treatment related adverse events. The safety results are summarized as follows.

The applicant reported that within 10 minutes after patch removal, no edema (Draize scores of 0) was observed at the anode site in most subjects; 99% (134/136) of subjects treated with the Northstar system and 95% (128/135) of subjects treated with the placebo system. In addition, within 24 (\pm 8) hours, no new cases of edema developed and all incidences of edema were resolved. The distribution of edema scores following patch removal between treatment groups was not statistically significant (p-value = 0.607) within 24 (\pm 8) hours of patch removal no edema (Draize scores of 0) was observed at the cathode site in 78% (106/136) of subjects treated with the Northstar system and 73% (99/135) of subjects treated with the placebo system. Further, no new cases of edema developed and all incidences of edema were resolved at the 24 hour visit. The distribution of edema scores between treatment groups was not statistically significant (p-value = 0.074). However, there were numerically higher incidence of edema in Northstar treated group than the placebo treated group.

The applicant reported that within 10 minutes of patch removal, no erythma was observed at the anode site in 67% (91/136) of subjects treated with the Northstar system compared with 73% (98/135) of subjects treated with the placebo system. The distribution of erythma scores between treatment groups was not statistically significant (p-value 0.528). At the 24 (\pm 8) hours post-treatment assessment, no erythma (Draize scores of 0) was observed at the anode site in 95% (126/133) of subjects treated with the Northstar system and 98% (126/128) of subjects treated with the placebo system.

There were three new cases of very slight erythma (Draize scores of 1) that presented at the 24 (\pm 8) hour assessment. The distribution of erythma scores did not differ between two treatment groups (p-value = 0.291).

The number of subjects who experienced at least 1 treatment-emergent AE was low and comparable between treatment groups: 12% (16/136) of subjects treated with the Northstar system and 13 (17/135) of subjects treated with the placebo system. The incidence of treatment-emergent AEs considered by the Investigator to be related to the study drug/device was also low and comparable between the Northstar and placebo groups.: 6% (8/136) of subjects treated with the Northstar system and 7% (9/135) of subjects with the placebo system.

A total of 10 (4 Northstar, 6 placebo) subjects experienced treatment-emergent AEs that led to discontinuation from the study. Treatment-related AEs that led to discontinuation occurred in 3% (4/136) of subjects treated with the Northstar system and 4% (6/135) of subjects treated with the placebo system. In all 7 subjects, incomplete delivery of the Northstar system or placebo system was indicated by the incomplete delivery light being illuminated on the controller. There were no adverse events associated with technical failure of the patch. Each of the subjects had an adhesion score of 0 (90% to 100% adhered, essentially no lift off the skin). No subjects experienced serious treatment-emergent AEs, and no subject died during the study.

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2.3.4 STATISTICAL REVIEWER'S FINDINGS

Study BDTS-9967:

The applicant's efficacy analyses (Table 2) were validated by this reviewer and the results were consistent. The results demonstrated that the subjects treated with the Northstar system reported significantly less pain associated with the venipuncture or IV cannulation compared with subjects treated with placebo system. The applicant did not conduct any tests for treatment by sub-group interactions. This reviewer conducted tests for interaction between treatment groups and subgroups (e.g., gender, race, age-group and site) using ANOVA model. All these tests failed to detect any interaction between treatment and each subgroup.

Study BDTS-99-68:

The applicant's efficacy analyses (Table 6) were validated by this reviewer and the results were consistent. The reviewer also conducted tests for interaction between

treatment and subgroups (e.g., gender, race, age-group and site) using ordinal logistic regression model. All these tests failed to detect any interaction between the treatment groups and each subgroup.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Study BDTS-99-67:

Subgroup analyses of VAS scores by both race and gender showed that, in all subgroups analyzed, subjects receiving treatment with the Northstar system reported feeling less pain immediately after the procedure than subjects receiving treatment with placebo. Subgroup analyses of VAS scores by age (<65 years and ≥ 65 years) showed that in both age categories subjects receiving treatment with the Northstar system reported less pain immediately after the procedure than subjects receiving treatment with placebo.

Study BDTS-99-68:

NFIS, weighted NFIS, and VAS scores indicated that children ages 5 to 17 years treated with the Northstar system experienced significantly less pain from the venipuncture/IV cannulation procedures than did subjects treated with the placebo system. There were no notable differences among the three age groups. In addition, subgroup analyses of NFIS (as well as weighted NFIS, and VAS) scores by both race and gender showed that, in all subgroups analyzed, subjects receiving treatment with the Northstar system reported feeling less pain immediately after the procedure than subjects receiving treatment with placebo.

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2.5 STATISTICAL AND TECHNICAL ISSUES

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2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The assessment of the efficacy of the Northstar system was based on the results of two pivotal, controlled studies and 15 supportive studies. A total of 536 subjects were treated and evaluated for the efficacy in the two pivotal studies. Study BDTS-99-67 tested the Northstar system in adults ≥ 18 years of age, and study BDTS-99-68 evaluated the Northstar system in children 5 to 17 years of age. Both studies compared the performance of the Northstar system (administering lidocaine 10% and epinephrine 0.1%) with placebo (an iontophoretic drug delivery system administering saline and epinephrine 0.1% only) and evaluated the _____ in preparation for venipuncture or IV cannulation. The results of these studies demonstrated that both adults and children treated with Northstar system experienced significantly less pain associated with venipuncture or IV cannulation compared with subjects treated with the placebo system.

2.7 CONCLUSIONS AND RECOMMENDATIONS

Efficacy:

Study BDTS-99-67:

Subjects treated with the Northstar system experienced significantly less pain from the venipuncture/IV cannulation procedures than did subjects treated with placebo system with (p-value < 0.001). Furthermore, a greater number of subjects treated with Northstar system (83%) reported feeling little or no pain (VAS score of 0 or 1) in contrast to subjects treated with the placebo system (32%).

Study BDTS-99-68:

NFIS scores indicated that subjects treated with the Northstar system experienced significantly less pain from the venipuncture/IV cannulation procedures than did subjects treated with the placebo system (p-value < 0.001). The assessment of pain by the parent(s)/guardian(s) immediately following the procedures was consistent with the NFIS scores assessed by the subjects themselves.

Safety:

Study BDTS-99-67:

The Northstar system was well tolerated as demonstrated by the low frequency of treatment related AEs. The dermal effects of the Northstar system, including edema and erythma, were minimal and transient in nature. In summary, this study indicates that the Northstar system is a safe and effective way to decrease the pain experienced by the adult subjects undergoing routine venipuncture or IV cannulation.

Study BDTS-99-68:

The number of subjects who experienced at least 1 treatment-emergent AE was low and comparable between treatment groups. The incidence of treatment-emergent AEs considered by the Investigator to be related to the study drug/device was also low and comparable between the Northstar and placebo groups. The dermal effects of the Northstar system, including edema and erythma, were minimal and transient in nature. In summary, this study indicates that the Northstar system is a safe and effective way to decrease the pain experienced by pediatric subjects undergoing routine venipuncture or IV cannulation.

Overall Conclusions:

The results demonstrated that both adult subjects and children ages 5 to 17 years treated with the Northstar reported significantly less pain associated with venipuncture or IV cannulation compared with subjects treated with the placebo system. In addition, the study indicates that the Northstar system is a safe to decrease the pain experienced by the adult subjects and pediatric subjects undergoing routine venipuncture or IV cannulation

Concur: Dr. Permutt

Mushfiqur Rashid, Ph.D.
Mathematical Statistician

2.8 APPENDIX

2.8.1 INDIVIDUAL STUDIES REVIEWED

Table A.1: Summary of Demographic and Baseline Characteristics (all randomized patients) in BDTS-99-67

Characteristics	Norhstar (N=137)	Placebo (N=139)	Overall (276)
Gender (n[%])			
Male	45 (33)	51 (37)	96 (35)
Female	92 (67)	88 (63)	180 (65)
Age (years) (n[%])			
<65	118 (86)	119 (86)	237 (86)
≥65	19 (14)	20 (14)	39 (14)
Race (n[%])			
Caucasian	101 (74)	105 (75.5)	206 (74.6)
Black	30 (22)	18 (20.1)	58 (21.0)
Hispanic	1 (1)	2 (1.4)	3 (1.1)
Oriental	1 (1)	1 (0.7)	2 (0.7)
American Indian	0	0	1 (0.4)
Other	4 (3)	2 (1.4)	6 (2.2)
Procedure Planned			
Venipuncture	70 (51.1)	70 (50.4)	140 (50.7)
IV Cannulation	67 (48.9)	69 (49.6)	136 (49.3)

Table A.2: Summary of Demographic and Baseline Characteristics in Study BDTS-99-68

Characterstics	Norhstar (N=136)	Placebo (N=136)	Overall (N=272)
Gender (n[%])			
Male	73 (54)	73 (54)	146 (54)
Female	63 (46)	63 (46)	126 (46)
Age(years) (n[%])			
5-7	38 (28)	34 (25)	72 (27)
8-11	48 (35)	50 (37)	98 (36)
12-17	50 (37)	52 (38)	102 (38)
Mean	10.2	10.4	10.3
Sd	3.56	3.42	3.48
Median	10	10.0	10.0
Procedure Planned			
Venipuncture	75 (55)	77 (57)	152(56)
IV Cannulation	61 (45)	59 (43)	120 (44)

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