

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-504

MEDICAL REVIEW(S)



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: May 6, 2004

DRUG: LidoSite Topical System [LidoSite Patch (lidocaine HCl/epinephrine topical iontophoretic patch) 10%/0.1% and LidoSite Controller]

NDA: 21-504

NDA Code: Type 3S NDA

SPONSOR: Vyteris, Inc.

INDICATION: For use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions

The Division took an approvable action on NDA 21-504 on July 25, 2003. The deficiencies in the application were clearly outlined in the approvable letter and focused primarily on the clarity of the clinical safety data, inadequate CMC components (summarized in my approvable memo of July 25, 2003) and labeling concerns. In addition, the manufacturing site for the LidoSite Patch was not available for inspection at the time of that action. A complete response to the approvable letter was received on November 10, 2003.

While the sponsor had clearly established the efficacy of their product in the initial application, the clinical review team revised the label to reflect a narrower indication than that requested by the sponsor based on the design and results of some of the clinical trials. The sponsor has agreed to the revised indication.

During the first review cycle, the clinical team noted that dermal sensitization and irritancy studies should be performed by the sponsor in order to address the frequent skin reactions and the preclinical dermatologic abnormalities. However, in light of the mixed preclinical results, and the reasonably informative clinical data from the repeat-application study, these studies are not likely to provide any additional useful data and will not be required at this time.

In his review dated April 24, 2004, Dr. Arthur Simone has determined that the sponsor has adequately addressed the Division's concerns regarding the safety data that were raised in the first cycle reviews and in the approvable letter. He has concluded that the product appears to be safe and effective. The sponsor has requested a deferral for studies in pediatric subjects less than 5 years of age. The Division has agreed to grant that deferral in order to collect post-marketing data on the approved pediatric population of children 5 years of age and older prior to moving into the younger, more vulnerable population.

In their recommendations dated March 12, 2004, the Office of Compliance reported that all manufacturing and testing facilities have achieved an acceptable level of cGMP compliance. In his review dated April 30, 2004, Dr. Ravi Harpanhalli has determined that the sponsor has adequately addressed all of the CMC deficiencies raised in the first cycle reviews and in the approvable letter. He has recommended product approval.

Finally, the Division and the sponsor have reached agreement on labeling for both the package insert and the carton and container.

I concur with the assessments and conclusions of the clinical and CMC review teams.

This application was filed under section 505(b)(2) of the Act. The only discipline that relied upon literature or a previous agency finding of safety or effectiveness to establish the safety or efficacy of this product was the pharmacology/toxicology team. The review by Dr. Timothy McGovern notes that no general toxicity studies were performed and refers to literature and "generally accepted knowledge" regarding the drug components lidocaine and epinephrine. He does reference NDA 20-530, Iontocaine, in support of the reproductive toxicology assessment, but a thorough literature review was also completed and served as the basis for his determination of Pregnancy Category B and for my concurrence with that determination.

Dr. McGovern also mentions NDA 19-941, EMLA Cream, in his discussion of a carcinogenic metabolite of lidocaine. However, information regarding the carcinogenicity of the lidocaine metabolite 2,6-xylidine is widely discussed in the pertinent literature and reference to NDA 19-941 was not essential to his assessment or to my decision to approve this NDA.

The clinical section of the application was complete and did not require reference to any approved drug product. The package included adequate and well-controlled clinical trials and a safety database that was considered by the review team to be appropriately sized

for this product. Of note, the sponsor's actual RLD for the drug components of their product was NDA 6-488 (Xylocaine with Epinephrine). The sponsor also referenced NDA 20-530 (Iontocaine) for their patch delivery system. They have certified that approval of their product will not infringe on any existing patents for the referenced products.

Action: Approval

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/s/

Bob Rappaport
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MEDICAL OFFICER

Clinical Review and Evaluation

NDA# (serial):	21-504 (N-000-AZ) 21-504 (N-000-BM)
Drug Name (generic):	LidoSite Lidocaine Iontophoretic Drug Delivery System (10% lidocaine HCl and 0.1% epinephrine bitartrate)
Sponsor:	Vyteris, Inc.
Indication:	To provide local dermal anesthesia on normal intact skin
Type of Submission:	Amendment to NDA – response to deficiencies
Date of Submission:	November 8, 2003 March 27, 2004
Date of Receipt:	November 10, 2003 (CDER stamp dates) March 29, 2004
PDUFA due date:	May 10, 2004
Reviewer:	Arthur Simone, MD, PhD
Project Manager:	Kimberly Compton
Review Date:	April 23, 2004

Background:

On July 25, 2003, FDA issued an approvable action regarding the LidoSite Lidocaine Iontophoretic Drug Delivery System. Thirty four deficiencies were noted in the action letter; the majority of which were related to chemistry and manufacturing issues. Five clinical issues were cited and have been addressed by the Sponsor in this submission. On review, additional information was requested regarding the response to the second clinical issue. This information was provided in the submission dated March 27, 2004.

Responses to Clinical Deficiencies:

The five clinical deficiencies, the Sponsor's responses and commentary on each are listed below.

Item 1:

Provide an explanation for the high incidence of high skin impedance in study 98NS-01-10.

Sponsor's Response:

The controller used in this study was a prototype that was set to deliver a current of 1.77 mA and had a maximum voltage output of — When skin impedance was so high (greater than the equivalent of 14.124 k Ω) that the voltage could no longer be adjusted to maintain the desired current, a “high impedance” condition resulted. As a result of these findings, the controller was changed to deliver up to 35 V in order to deliver the desired 1.77 mA. The controller with the 35 V limit was used in all Phase 3 clinical studies and is the device intended for commercialization.

Comment:

The response satisfies the deficiency. Because the controller with the 35 V maximum voltage output was used in all the Phase 3 studies and was intended as the to-be-marketed product, initiation of its use part way into product development should not adversely affect either the safety or efficacy evaluations of the product. As the iontophoretic delivery of drug depends only on the current applied and the duration of its application, systemic levels of drug should not be affected by the change in maximum voltage.

Item 2:

Provide an explanation for the high incidence of papular rash in study BDTS-00-57.

Sponsor's Response:

The intent of the study was to monitor post-treatment reactions after application and removal of the LidoSite patch. The site conducting the study had issues with respect to training, which affected the capturing of adverse events. Several instances of papules were documented as having occurred on a number of subjects. The description of the skin reaction was not clear and made it difficult to verify whether these skin reactions were adverse events (AEs). The skin reaction descriptions should have included information about the dimensions of the reaction; the topography of the reaction; the time course of the reaction; the extent of the reaction; the presence or absence of subjective symptoms associated with the lesions; the location of the reaction relative to the experimental treatment.

The information obtained from this study was applied in the training of clinical personnel in evaluation of adverse events during subsequent studies. The Sponsor notes that after this study, five studies, including all Phase 3 trials, were conducted with more than 700 subjects and no incidents of papules were observed.

Comment:

The Sponsor did not provide specific information as to the assessments of subjects in this study. It is not clear if the Investigators were inaccurate in their reporting, unclear as to the meaning of the terms used to describe possible skin reactions, or overzealous in their reporting of findings. While the consistency of subsequent studies in terms of dermatological findings is somewhat reassuring, it must be determined that this occurred with careful inspection and uniform application of descriptors rather than from less rigorous assessments or changes in descriptions applied to various skin reactions. The Sponsor was requested, on March 2, 2004, to provide a list of specific problems that were encountered in study BDTS-00-57 when skin assessments

were made, and to provide a detailed description of the training provided for skin evaluations in subsequent studies. In a submission dated March 27, 2004, the Sponsor provided the information requested.

Sponsor's Second Response:

For Study BDTS-00-57, the skin assessments were conducted by personnel who do dermal assessments of topical products such as sunscreens, deodorants, and antiperspirants. These personnel were trained internally to assess reactions related to these types of products, but for this study, they were trained by Becton Dickinson Clinical Trials Resource personnel to assess skin reactions typical of iontophoretic drug delivery. Skin assessments were subjective; Draize scoring was used post-treatment, although not for the assessment made immediately after iontophoretic treatment. Non-erythema or edema findings were listed as "untoward skin reactions" and included comments describing the findings. The Sponsor states that "(I)n subsequent studies (BDTS-99-67, BDTS-9968, BDTS-00-16, BDTS-00-17, VYTERIS-01-01) conducted after BDTS-00-57, the subjective skin evaluation was replaced with a skin evaluation performed using Draize scoring."

The Principle Investigator, Joy Frank, R.N., indicated in the final study report that "none of the adverse events reported were considered to be serious." In addition, the Sponsor noted that the Principle Investigator, in a telephone conversation with a Clinical Research Specialist at Becton Dickinson and Company, raised the issue on November 8, 2000, and followed it up with a letter dated November 9, 2000. The key points from the interactions included:

- The papule-like eruptions appeared mild and transient in nature.
- The papule observations were a "normal dermal effect" and should not be considered an unusual outcome.
- Completion of an adverse event document was unnecessary for such occurrences.

It was noted that the Study Safety Monitor, Seymour Schlager, M.D., after review of the Case Report Forms, requested that the appearance of papules at the contact site be considered adverse events. In subsequent studies, only Draize score evaluations and dermal assessment for burns were performed.

Comment:

It would have been preferred that the Sponsor continued assessing treatment sites for rash-like reactions. The use of the Draize scale and an assessment for burns at the treatment sites are inadequate when used alone to describe the numerous reactions that may occur. The mild nature of the papular-rash reaction and its brief duration suggest, however, that it is not an issue for significant safety concern. As the innovator product reported rash in 1% of patients, and for Study BDTS-00-57, rash was noted in 11% of subjects

Item 3:

Provide an explanation for defining burns as a Draize erythema score of 4 (a serious adverse event by your definition), but then reporting no serious adverse events despite multiple reports of burns, including at least one 2nd degree burn, related to use of the patch.

Sponsor's Response:

In all the clinical studies, the following outcomes were defined as Serious Adverse Events (SAEs).

- Death
- Life-threatening (refers to any event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe)
- Persistent or significant disability or incapacitation (refers to any event which results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions)
- Hospitalization or prolongation of a hospital stay
- Congenital anomaly/birth defect
- Important medical event that may require intervention to prevent one of the preceding conditions

Based on the above definitions, there were no SAEs in any of the clinical trials. Dermal effects occurring subsequent to the application of an iontophoretic treatment were captured using a Draize scale and included in the safety evaluation of the drug product. The Draize scale allowed evaluation of erythema and edema at the application site which were assessed immediately on removal of the iontophoretic patches, as well as at 1, 24, and if needed, 48 hours later. Subjects with a Draize scale score of 4 for erythema ["Severe Erythema – beet redness to slight Eschar formation (injuries in depth)"] were further evaluated for burns. An erythema score of 4 or the presence of 2nd degree burns, as observed in the studies, did not qualify as a SAE.

Comment:

The above response is acceptable and consistent with the commonly accepted definition of SAE. The capturing and reporting of burns as part of the safety evaluation are adequate to assess overall safety of the drug product and to determine appropriate labeling.

Item 4:

Provide an accounting for skin reactions not previously reported as AE's, e.g., in study 98NS-01-09, subject #915 had burns at all four application sites and subject #923 had skin removed by the patch adhesive at all four application sites per the DERMAL dataset, yet the adverse events dataset (ADVRE) contained none of these events.

Sponsor's Response:

Complete case report forms (CRFs) for the two subjects in question were included with the response.

Regarding subject #915, an adverse event occurred at the site of the cathode on the right arm. Specifically, a lesion that was rated as a 3 on the Draize scale for erythema was observed

immediately after patch removal. The Draize scores for the same site were “0” at one and 24 hours following patch removal. On the CRF, a note was recorded on the DERMAL EVALUATIONS section which stated, “RA cathode burn resolving. Appears to be very superficial.” The comment was made for only the one site although each subject received four treatments, each at a different site. The entry of the same comment at each of the four sites in the “Dermal” dataset corresponding to this study was a result of an error in data entry and has been corrected. A revised “Dermal” data set for this study is included with this submission.

For subject #923, “L-A adhesive from patch removed some skin. Picture taken,” was noted on the 24 hour dermal evaluation form DERMAL REACTIONS. The comment was noted for only one site at the left antecubital fosse (LA) and not four sites as described. Each subject in this study received four treatments, each at a different site. A subsequent query also included with the CRF was generated by the clinical research associate (CRA) to verify whether the noted event was an adverse event or not and the resolution to the query was “disregard query” indicating that the event was not an adverse event. The Principle Investigator reviewed and signed the Adverse Event and Final Evaluation case report forms after the query was resolved.

Comment:

The information provided for subject #915 was verified by review of the CRFs. The Sponsor’s response satisfies the issue raised. The comment, “L-A adhesive from patch removed some skin. Picture taken,” was listed four times in the dermal reactions file for subject #923 at the 24-hour follow-up evaluation. This comment was repeated at each test site: left hand, right hand, left arm and right arm, and it only occurs at the 24-hour evaluation. The Sponsor’s response suggests that the “L-A” stands for left arm or more precisely, left antecubital fossa. This is supported by the CRF copy of the comment where L-A is used elsewhere on the same page to distinguish the left antecubital fossa test site. Thus, if the reaction occurred at all, it was likely to have occurred only at the L-A site. The query resolution form for this subject states, “LA records adhesive from patch removed some skin. Why wasn’t this considered an EAE?” The query is crossed off and “Disregard” is written in the resolution box along with the initials of the CRA who completed the form and the date: 8/18/98. As there were no pictures found to substantiate an injury, the CRFs support, at worse, one site of injury. The injury was only noted a day after the treatment was given and the CRA indicated the remark should be disregarded, it is therefore reasonable to assume the injury did not occur and to revise the “Dermal” dataset accordingly. Thus, the adverse event file for this study is accurate as initially submitted.

Item 5:

Retabulate the adverse events tables to include the points below as to allow for more appropriate product labeling.

- a. Pain: Retabulate AE’s to include all pain in one category with subcategories to include “pain NOS” and all unpleasant sensory AE’s such as “application site burning” unless justification is provided otherwise. Resolve these events into those temporally associated with patch application, patch removal, procedure, and post-procedure.
- b. Burns: Justify creation of a separate “burns NOS” category and define entry to this category. Retabulate AE’s to include all burns in one category with subcategories to include burns NOS.

- c. All skin reactions: Present a tabulation of all skin reactions, with subcategories including rashes, erythema, burns, pallor/blanching, hematoma, sunburn, dermatitis, pruritus, etc.
- d. Placebo groups: retabulate integrated AE tables with separate incidence columns for “passive” placebos (i.e., no current) and for “active” placebos (with current).
- e. Provide a comprehensive tabulation of adverse events for all studies of MIP II and III

Sponsor’s Response:

In order to address all the issues identified, a database integrating all the adverse events (AE) observed during clinical studies involving the MIP II and MIP III designs was constructed. This was accomplished by integrating the AE dataset from the Integrated Safety Summary (ISS) with the AE datasets from additional clinical studies, i.e., early Phase I clinical studies that were not part of the ISS but were conducted with MIP II and MIP III patches. The new AE dataset, “mip2and3AE,” has additional variables to enable a breakdown of the dataset by the type of study, type of placebo, type of patch, and the timing of the AE relative to patch application, removal, or procedure.

To address items 5 (a), (b) and (c), several MedDRA classifications of the AEs were revised as follows.

- The “Pain NOS” AEs that occurred during the patch application or procedure were reclassified as “Application Site Pain.”
- The “Pruritus NOS” was reclassified as “Application site Pruritus.”
- The “Urticaria NOS” was reclassified as “Application site Urticaria.”
- The “Erythema NEC” and “2nd degree burn” – all of which occurred at the site of application were reclassified as “Application site burn.”

The timing of the AE relative to patch application or removal or relative to the procedure was determined based on actual timing of the AE when available or determined by the actual text used to describe the AE. For example, “burning at the patch site” was included as occurring during patch application, i.e., the time that the patch was on the skin.

For the Phase I clinical studies with multiple treatments, treatment classification was labeled as Multiple Treatments and couldn’t be separated into Active or Passive Placebo or Northstar treatment, because a subject could have received two of the treatments. Also in clinical studies with multiple treatments, if the time information associated with the AE was not captured in the CRF, due to the design of the CRF, it was not feasible to determine the occurrence of the AE relative to which treatment application, i.e., whether associated with the active treatment or the placebo treatment. In addition, there was one study, BDTS-99-25 (one of the studies with multiple treatments), which involved the use of both active and passive placebo along with the Northstar system and another study, 98NS01-09 (also a study with multiple treatments), which involved the use of both MIP II and MIP III patches. All of these studies were early Phase I studies. Combined, these last two studies accounted for seven adverse events.

The data from the new AE dataset, i.e., mip2and3AE, were analyzed to create pivot tables to address the Division’s requests in Item 5(a) through 5(e). Four tables were created and were labeled as:

1. Adverse Events by Body System and Preferred Term
2. Adverse Events Possibly or Probably Related to the Study Drug/Device by Body System and Preferred Term
3. Adverse Events by Body System and Preferred Term for Pain, Burns, and Skin Reactions
4. Adverse Events (Pain, Burns, and Skin Reactions) Possibly or Probably Related to the Study Drug/Device by Body System and Preferred Term.

The above tables present the adverse events categorized by the type of study, MIP II versus MIP III, active placebo versus Northstar treatment, and by the timing of AE relative to patch application, patch removal, during procedure, post procedure, or other.

In clinical study 98NS01-08, for subjects #1 and #11, the AE occurred on the day of the skin impedance assessment, which was done approximately two weeks prior to the start date of the study treatments.

Comment:

Twenty-two treatments were listed as “Multiple Treatments” with no way of delineating whether the adverse events were related to placebo or Northstar treatments. The adverse events for this group included six incidents of burns, four non-specific ECG changes, two incidents of hypertension, two incidents of “pain where heplock is,” and one incident each of: 102 degree fever, light headedness, low blood pressure, cold sweats, sore throat, numbness of a finger, nausea/vomiting, and dermatitis. Of all these adverse events, the ones most likely related to iontophoretic treatment and of clinical significance are the burns. A second review of the final study report of BDTS-99-25 indicated that four burns occurred with the Northstar treatment and one with active placebo. A second review of the final study report for trial 98NS-01-09 provided no further information on the MIP number of the patch involved with the burn, or on whether it was a placebo or Northstar treatment. If the data with known sources are included in the table of most frequently observed adverse events from all studies involving LidoSite™, the incidents of LidoSite™ burns increases from 9 to 13 (1% to 1.4%) and the incidents of placebo burns for LidoSite™ without lidocaine increases from 0 to 1 (0% to 0.3%). These changes do not impact significantly on the safety of the system, and the number of unknown treatments resulting in a burn has been reduced to one which similarly would not significantly alter the safety assessment regardless of the nature of that treatment.

The adverse event data set and the summary data tables presented with the submission include the requested information and should be sufficient to provide adequate labeling for adverse events. Initial review of the AE dataset suggests that inclusion of the studies not previously incorporated into the ISS will not significantly affect the overall safety profile of the product. This item can therefore be considered adequately addressed once the label has been updated.

Final Item:

Additionally, the Sponsor was to include a safety update as described in 21 CFR §314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

Sponsor's Response:

The Sponsor reported that there are no open studies and no additional safety information to report at this time. The last Phase 3 study was concluded March 1, 2002, and the final study report was submitted with the NDA.

Comment:

The Sponsor's response is sufficient and satisfactory.

Comments and Recommendations:

The Sponsor has satisfactorily addressed all the clinical issues noted in the review of the original NDA submission. The NDA has provided sufficient data to allow determination that the LidoSite system is safe and effective for use in .

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/s/

Arthur Simone
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MEDICAL OFFICER

Nancy Chang
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH

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DIVISION DIRECTOR'S ACTION M E M O R A N D U M

DATE: July 25, 2003

TO: File, NDA 21-504

FROM: Bob A. Rappaport, M.D.
Director (Acting)
Division of Anesthetic, Critical Care and Addiction Drug Products

RE: Northstar Lidocaine Iontophoretic Drug Delivery System

Background

The original IND (48,365) for what was then called the Lidocaine Iontophoretic Delivery System was submitted by Becton-Dickinson on July 14, 1995. In November of 2000, sponsorship was transferred to Drug Delivery Technologies, Inc. In March of 2001, the sponsor's name was changed to Vyteris, Inc.

NDA 21-504 was initially submitted on May 9, 2002 as a 505(b)(2) application. The application was withdrawn prior to the filing deadline when the Division discovered errors in data entry, uninterpretable formatting of data, and insufficient definition tables. The application was resubmitted on September 25, 2002 and found to be acceptable for filing by the Division.

The Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar System) is an iontophoretic device that provides dermal anesthesia via transcutaneous delivery of lidocaine HCl in combination with epinephrine. The system is composed of a drug-filled patch connected to a direct current source (the controller), with both the anode and cathode assemblies residing in the single patch. The drug product (lidocaine HCl 100 mg and epinephrine 1.05 mg) is contained in a reservoir at the anode, while the cathode reservoir contains an electrolyte solution that completes the electrical circuit for return of

current. The controller provides a total charge of 17 mA•min (3.4 mA•min/cm²) over a 10-minute interval.

The clinical portions of this application were reviewed in thorough detail by Arthur Simone, M.D., Ph.D. under the supervision of Nancy Chang, M.D. This memo will serve to summarize their review, as well as the reviews written by the other member of the team: Mushfiquir Rashid, Ph.D., biostatistics; David Lee, Ph.D., biopharmaceutics; Timothy McGovern, Ph.D., pharmacology/toxicology; Ravi Harapanhalli, Ph.D., chemistry, manufacturing and controls (CMC); and Kevin Lee, M.D., CDRH devices consultant.

The clinical development program encompassed three generations of patch designs, referred to as Market Image Patch (MIP) I, II and III. The second and third generations of the MIP's were designed to improve delivery, dosing, safety, ease of use and battery life (see Dr. Simone's review, Table 4, page 21). The to-be-marketed Northstar System includes the MIP III patch.

The Northstar System has been evaluated in 1252 subjects in 17 clinical studies. The sponsor has requested the indication read as follows:

Efficacy

Two studies were defined as pivotal by the sponsor: BDTS-99-67 and BDTS-99-68.

BDTS-99-67

This was a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial that assessed the pain associated with either venipuncture or insertion of an intravenous cannula in adults patients presenting for one of those two procedures. The placebo patch contained saline and epinephrine and operated with the same electrical current as the active product. Pain was assessed immediately following the procedure using a 10-cm Visual Analogue Scale (VAS). One hundred and thirty-four subjects treated with the Northstar System and 136 subjects treated with the placebo system completed the study.

The primary efficacy analysis used an ANOVA to compare the mean VAS scores between the Northstar and the placebo groups. The VAS scores in the Northstar group (mean VAS score $\pm$ s.d. = 0.77 ± 1.5) were statistically significantly lower (less pain) than the scores in the placebo group (2.53 ± 2.3), with a p-value of less than 0.001.

BDTS-99-68

This was a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial that assessed the pain associated with either venipuncture or insertion of an intravenous cannula in pediatric patients (ages 5 through 17 years) presenting for one of those two procedures. The placebo patch contained saline and epinephrine and operated with the same electrical current as the active product. Pain was assessed immediately following the procedure using a Nine-Face Interval Scale (NFIS). Subjects over age 12 years also assessed pain on a 10-cm VAS and subjects less than 12 years additionally had their pain assessed by a parent or guardian using the NFIS. One hundred twenty-six subjects treated with the Northstar System and 123 subjects treated with the placebo system completed the study.

The primary efficacy analysis used an ordinal logistic regression model to compare the difference between the Northstar and the placebo groups in regard to the NFIS scores. Subjects treated with the Northstar System experienced statistically significantly less pain from the venipuncture/IV cannulation procedures than did subjects treated with the placebo system, with a p-value of less than 0.001. Table 24 on page 56 of Dr. Simone's review documents the numerical results by treatment group.

The sponsor also analyzed the NFIS scores broken down by age groups (5 to 7 years, 8 to 11 years, and 12 to 17 years). The results in all three categories were consistent with the overall results (see Table 25, page 57 of Dr. Simone's review). The two secondary analyses, the VAS scores in the older patients and the NFIS scores recorded by parent/guardian for the younger patients were also consistent with the primary efficacy analysis.

BDTS-00-16

Of the six other placebo-controlled studies evaluating either analgesia or depth of anesthesia (summarized in Dr. Simone's review), five had results consistent with Studies BDTS-99-67 and 68. However, Study BDTS-00-16, "Efficacy of the Northstar Iontophoretic Lidocaine Drug Delivery System for Anesthesia Prior to Treatment of Dermal Lesions by Laser," failed to show a statistically significant treatment effect for the Northstar System compared to a placebo system. Sixty-six patients completed the study. Seven pediatric subjects and 27 adult subjects were treated with the Northstar System, while 3 pediatric subjects and 29 adult subjects were treated with a placebo system.

The protocol-specified primary outcome analysis used an ANCOVA model to compare VAS scores. The VAS scores were weighted using the investigators' estimate of the percentage of the procedure that was completed at the time that any additional anesthesia was required. This weighted score was calculated using the following formula: VAS x

(1 + (1 – percent of procedure completed))¹. While the mean weighted-VAS scores were higher in the placebo group, the difference between the two groups was not statistically significant. A supplemental, post-hoc analysis using a non-parametric ranking of the unweighted-VAS scores performed by the sponsor did result in a statistically significant treatment effect. The sponsor contends that this result was driven by two of seven subjects treated with the Northstar System at the smaller center of the two centers who had VAS scores that were higher than the other subjects in that treatment group. The ranked VAS analysis reduced the deviations of the mean score within the treatment groups resulting in the significant difference.

Protocol specified secondary analyses included physician assessment using a VAS that also failed to find a statistically significant treatment effect, and a categorical assessment of pain that did find a statistically significant treatment effect. It is important to note that the only other study of the Northstar System's efficacy to provide anesthesia for the removal of dermal lesions was open-label and uncontrolled.

Safety—Preclinical

While there have been some reproductive toxicology results of concern in the preclinical literature submitted to the application, Dr. McGovern states in his review that, "In light of the observed low levels of clinical systemic exposure to lidocaine and epinephrine and the vast previous human experience with both compounds, the...potential developmental effects are not considered to be of clinical significance for the proposed drug product." (page 2 of Dr. McGovern's review)

The primary preclinical safety issue identified by Dr. McGovern is the potential for dermal effects at the patch treatment site. In one study, severe dermal irritation reactions at active patch sites were observed in Guinea pigs. However, more recent studies demonstrated that application of the to-be-marketed patch in a setting that mimics clinical use produced dermal irritation scores in New Zealand white rabbits that demonstrated a lack of irritancy potential. Histopathological assessments did show a mild inflammatory response in some muscle tissue in rabbits. Additionally, fourteen-day treatments did result in mild gross pathological changes in lidocaine-treated animals. Evaluation of delayed hypersensitivity in Hartley Guinea pigs demonstrated that the patch was non-sensitizing. Dr. McGovern has concluded that, "...the potential for dermal irritation has been adequately characterized in nonclinical models." (page 1 of Dr. McGovern's review)

Safety—Clinical

Safety data from 1143 subjects (812 Northstar System-treated and 331 placebo-treated) who received at least one application of the MIP III Northstar System or placebo system in four placebo-controlled and six open-label studies were integrated and summarized in

¹ Thus, the weighted-VAS score would be equal to the unweighted-VAS if the subject completed the procedure without supplemental analgesia, but would be double the unweighted-VAS if the subject required supplemental analgesia before the procedure could begin.

the sponsor's ISS database. Safety data from six other studies deemed by the sponsor to have designs that were not compatible with integration into the ISS database were also analyzed by Dr. Simone. Data from nine other studies conducted using the earlier prototypes of the Northstar system and from one prematurely discontinued study using the MIP III system were also reviewed by the clinical team.

A total of 1010 subjects/patients were exposed to the MIP III system. 168 additional subjects exposed to the MIP II system were included in Dr. Simone's safety review.

There were no deaths or serious adverse events reported for any trial during product development. In the placebo-controlled studies, 7 (2%) placebo-treated and 4 (1%) of Northstar-treated patients discontinued due to adverse events. These events included pain, application site burning, application site pain, and vasoconstriction. All occurred with equal or greater frequency in the placebo-treated subjects. All of these events resolved spontaneously. In the open-label studies, 0.6% of subjects discontinued due to an adverse event. Two of those subjects discontinued due to application site burning and one due to application site pain. All of the adverse events resolved spontaneously.

Adverse events overall occurred with a similar frequency in all subjects, regardless of treatment group or study design. For adverse events attributed to the active treatment, a higher percentage (10%) of subjects in the open-label studies experienced an AE compared with subjects in the placebo-controlled studies (4% of placebo-treated and 5% of Northstar System-treated).

In the controlled studies, pain "not otherwise specified" (NOS) was the most common adverse event in both treatment groups. However, the incidence was higher in the placebo-treated subjects (5%) than in the Northstar-treated subjects (2%)². While erythema, edema and blistering/papular rash at the application site were common, these adverse events were generally considered to be mild and resolved within 24 hours. Application site papules were the most common (8% of subjects) adverse event in the open-label studies. These occurred more frequently in pediatric patients ages 8 to 17 years.

Clinically significant burns primarily occurred with the earlier patch prototypes. However, one patient treated with the MIP III patch in Study BDTS 99-68 did develop a second degree burn under the wire to the cathode. This 13 year old Hispanic boy experienced resolution of the burn after 21 days. While there was a frequent occurrence of high impedance (25% of subjects) and resultant treatment failure in Study 98NS 01-09, no burn injuries occurred in this study.

One subject in Study 98NS-01-09 had skin removed by the patch adhesive at all four application sites. Further information regarding and an explanation for this event have been requested from the sponsor.

² It should be noted that interpretation of this result is difficult at best, as the sponsor did not delineate whether the pain that was recorded was due to the procedure (efficacy) or the treatment (adverse event).

The sponsor included multiple terms for pain and for dermal irritation. Dr. Simone reanalyzed the data by combining like terms for each of these domains. His analysis (see page 104 of his review) indicated that less pain was associated with the use of the Northstar system than with the placebo.³ However, considerably more dermal reactions occurred with the Northstar System.

As Dr. Simone has noted on page 88 of his review, there were two types of placebos used in different trials during the product's development. Some studies used a Northstar system without current while others used an active Northstar System that contained a drug formulation without the lidocaine component. All of the dermal adverse events seen in the placebo-treated subjects and all placebo-related adverse events occurred with the latter system.

Three additional studies conducted in healthy volunteers by _____ were not submitted with this application. The review team has requested that the sponsor provide the data from those studies, but that data has not yet been received.

Biopharmaceutics:

Studies BDTS-99-56 and BDTS-00-10 found that plasma samples of lidocaine were below the limit of quantitation, and, therefore, no pharmacokinetic parameters were calculated. The results of study Vyteris 01-01 documented that no subject had an epinephrine concentration above 50 pg/mL, indicating that the Northstar System did not result in additional epinephrine to the systemic circulation.

Chemistry, Manufacturing and Controls:

The 510K (K031551) for the controller is currently being reviewed in CDRH by Kevin Lee, M.D.

The electrode subassembly and the electrical specifications of the patch were evaluated via consult by CDRH reviewer Kevin Lee, M.D. Dr. Lee determined that the manufacturing process and specifications for the iontophoretic patch, the pouch container closure, the pH hydrogen surface of the anode and cathode, the anode-specific capacity of the anode and cathode, the dielectric leakage current, the patch leakage current, the patch conductance, the hydrogel/electrical conductivity of the anode and cathode, and the overall container closure were acceptable.

³ It should be noted that interpretation of this result is difficult at best, as the sponsor did not delineate whether the pain that was recorded was due to the procedure (efficacy) or the treatment (adverse event).

An IR letter was sent to the sponsor on May 2, 2003. A number of issues delineated in that letter have since been sufficiently addressed by the sponsor. However, several important CMC issues related to product quality remain unresolved. These issues are enumerated below:

1. Pre-approval Inspection

In the original NDA submission, Becton Dickinson Medical Systems (BDMS) was identified as the contract manufacturer of the bulk electrode solutions. However, during this review cycle BDMS informed Vyteris, Inc. of their intent not to continue production of the two bulk electrode solutions. Thus, Vyteris is moving the manufacture of the bulk electrode solutions to their facility in Fair Lawn, New Jersey. In a teleconference on March 12, 2003, Vyteris requested that the Agency defer the inspection of their manufacturing facilities until July, 2003. However, the production of a test batch of the drug product following equipment installation at the new manufacturing site could not be completed by the user fee date. At the time of this action, the new facility is still not ready for inspection and the sponsor reports that they anticipate being prepared for inspection in September, 2003. Additional stability data from the Vyteris site is also required and will not likely be available until 3rd quarter 2003.

CDER and CDRH Offices of Compliance determined that the potential need to inspect the manufacturer of electrode subassembly should be assessed after the inspection of Vyteris, the manufacturer of the finished patch.

2. Drug Product Assay and Impurity Specifications

Adequate specifications for assay and impurities for the active components in the drug product have not been provided.

3. Drug Product In-use Stability Data

Data for the chemical stability of the lidocaine and epinephrine in the drug product during the 10-minute patient use have not been provided; the electrical current during iontophoresis may degrade the drug substances.

4. Drug Product Stability

Drug product stability trends of concern include declining trace conductance and increasing peripheral probe tack. There were several instances of skin damage associated with patch removal that may have been related to increased probe tack over storage. Instances of patient withdrawal due to high impedance may be related to declining trace conductance. The sponsor submitted _____ of stability data and proposed _____ expiration dating period. Due to the concerns over the trends on stability, the lack of analysis of these trends, the lack of justification for appropriate acceptance criteria for these attributes, and the lack of _____ real-time data, the appropriateness of the proposed expiration dating period of _____ cannot be assessed and furthermore the appropriateness of a shorter expiration dating cannot be assessed.

5. In-process Manufacturing Tests

A sampling plan for the in-process tests, representative of the patch manufacturing process, has not been submitted. Without this information, the adequacy of the controls over the manufacturing process cannot be assessed

6. Electrode Subassembly Manufacturing

Information on the manufacture of the electrode subassembly has not been submitted. Without this information, the continued effectiveness and quality of the drug product cannot be assessed.

7. Crystallization of Drug

As the electrode solution is formulated close to the solubility of lidocaine HCl, and the presence of glycerine and other ingredients could reduce the solubility of this active component, data on potential crystallization upon cooling, and its impact on product performance is necessary. This has not been addressed in the submission.

8. Lack of an in vitro or in vivo drug release method:

A drug release test (in vitro or in vivo) to measure the product performance has not been provided. The absence of a test for drug release presents difficulty in assessing and assuring the adequate performance of the drug product at release and assessment of its expiration-dating period.

9. Inadequate DMF's

The DMF's for _____ were inadequate to support the application. The drug substance specifications, the in-process controls, and the controls over the starting materials need to be revised in order to assure adequate purity of these drug substances.

Nomenclature:

The Division of Medication Errors and Technical Support in the Office of Drug Safety has reviewed the proposed proprietary name, "LidoSite," and has no objection to its use. The Division review team concurs with this opinion.

Comments:

The sponsor's manufacturing site was not available for inspection during the review period for this application. They expect to be prepared for inspection later this year. In addition, there are multiple CMC deficiencies that have been delineated above.

The sponsor has clearly established efficacy of their product for use in providing dermal analgesia for venipuncture and insertion of an intravenous catheter. However, they have

requested an indication that

Although there were few clinically concerning adverse events, the safety database was poorly organized and, thus, difficult to accurately evaluate. Retabulation of the safety data to allow for a clear assessment of the product's profile in comparison to the two different placebo treatments, and to allow for a more accurate assessment of the commonly occurring events of "pain" and "skin reactions," will be a necessary foundation for a final risk benefit analysis. Data from studies performed _____ and CRF's for subjects who discontinued studies due to adverse events have been requested from the sponsor.

As the preclinical dermal study results were mixed, and in light of the fact that the most common adverse events in the clinical trials involved skin reactions, it will be necessary for the sponsor to perform sensitization and irritancy studies. The design of these studies should be made as consistent as possible with that recommended by the FDA Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products.

Numerous changes to both the package insert and the package and container labeling have been recommended by the review team. These changes will be forwarded to the sponsor.

Action: Approvable

cc.Division File: NDA # 21-504, A. Simone, N. Chang, R. Meyer
cc.DFS: NDA # 21-504 (N000)

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

/s/

Bob Rappaport
7/25/03 09:11:38 PM
MEDICAL OFFICER
Approvable Memo



FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

REVIEW AND EVALUATION OF CLINICAL DATA

NDA#	21-504
Sponsor:	Vyteris, Incorporated
Generic Name:	Iontophoretic lidocaine with epinephrine
Proprietary Name:	Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar System)
Pharmacologic Class:	Local anesthetic
Proposed Indication:	"Northstar System™ is indicated for the — — —
Submission Date:	September 25, 2002
Clinical Reviewer:	Arthur Simone, MD, PhD
Statistical Reviewer:	Mushfiquir Rashid
Completion Date:	July 25, 2003

Table of Contents

TABLE OF CONTENTS.....	2
EXECUTIVE SUMMARY	5
1 RECOMMENDATIONS.....	5
1.1 Recommendation on Approvability.....	5
1.2 Recommended Phase IV Studies or Marketing Restrictions	5
1.2.1 Recommended Phase IV Studies	5
1.2.2 Recommended Marketing Restrictions	6
2 SUMMARY OF CLINICAL FINDINGS.....	6
2.1 Overview of Clinical Program.....	6
2.2 Efficacy	7
2.3 Safety.....	9
2.4 Dosing.....	11
2.5 Drug-Drug Interactions	11
2.6 Special Populations.....	12
PRIMARY CLINICAL REVIEW	13
1 INTRODUCTION AND BACKGROUND.....	13
1.1 Proposed Indications	13
1.2 Milestones in Product Development	13
1.3 Foreign Marketing	16
2 SIGNIFICANT FINDINGS FROM CHEMISTRY AND ANIMAL PHARMACOLOGY AND TOXICOLOGY	17
2.1 Chemistry	17
2.2 Pharmacology and Toxicology	18
3 HUMAN PHARMACOKINETIC AND PHARMACODYNAMICS	20
3.1 Pharmacokinetic and Pharmacodynamic Studies	20
3.1.1 Pharmacokinetic Studies	20
3.1.2 Summary of Drug Formulation Development.....	20
4 DESCRIPTION OF CLINICAL DATA AND SOURCES	22
4.1 Sources of Clinical Data	22
4.2 Overview of Clinical Trials	22
4.3 Postmarketing Experience	23
4.4 Literature Review	24
5 CLINICAL REVIEW METHODS AND DATA INTEGRITY	25
5.1 Conduct of Review	25
5.2 Materials Consulted in Review	25
5.3 Evaluation of Data Quality and Integrity.....	26
5.4 Conduct in Accordance with Accepted Ethical Standards	27
5.5 Evaluation of Financial Disclosure	27
6 REVIEW OF EFFICACY.....	28
6.1 Brief Statement of Conclusions	28
6.2 Approach to Review of Efficacy	28
6.3 Review of individual, controlled studies contributing to conclusions of efficacy.....	29
6.3.1 Study BDTS-99-67: A Double-blind Evaluation of the Northstar Lidocaine Iontophoretic Drug Delivery System in Adult Subjects.....	29
6.3.1.1 Overall Design and Summary of Findings.....	29
6.3.1.2 Study Plan.....	30
6.3.1.3 Objectives	30
6.3.1.4 Design.....	30
6.3.1.5 Primary Efficacy Variable	30
6.3.1.6 Population.....	31
6.3.1.7 Methods and Procedures.....	32

6.3.1.8	Analysis Plan.....	34
6.3.1.9	Protocol Amendments	35
6.3.1.10	Study Conduct.....	36
6.3.1.11	Demographics/Group Comparability.....	38
6.3.1.12	Treatment Compliance	40
6.3.1.13	Unplanned Analyses.....	40
6.3.1.14	Sponsor's Efficacy Results.....	41
6.3.1.15	Discussion of Efficacy Findings in Study BDTS 99-67	42
6.3.2	BDTS-99-68 A Double-blind Evaluation of the Northstar Lidocaine Iontophoretic Drug Delivery System in Pediatric Subjects	43
6.3.2.1	Overall Design and Summary of Findings.....	43
6.3.2.2	Study Plan.....	44
6.3.2.3	Objectives.....	44
6.3.2.4	Design.....	44
6.3.2.5	Primary Efficacy Variable	44
6.3.2.6	Secondary Efficacy Variables.....	45
6.3.2.7	Population.....	45
6.3.2.8	Methods and Procedures.....	46
6.3.2.9	Analysis Plan.....	48
6.3.2.10	Protocol Amendments and Changes in the Planned Analysis.....	50
6.3.2.11	Study Conduct.....	51
6.3.2.12	Demographics/Group Comparability.....	53
6.3.2.13	Treatment Compliance	55
6.3.2.14	Unplanned Analyses.....	55
6.3.2.15	Sponsor's Efficacy Results	55
6.3.2.16	Discussion of Efficacy Findings in Study BDTS 99-68	59
6.3.3	Other Controlled Clinical Studies	61
6.3.3.1	BDTS-99-24 Dermal Depth of Anesthesia Produced by the Northstar Iontophoretic Lidocaine Drug Delivery System	61
6.3.3.2	BDTS-99-25 In-House Evaluation of a Developmental Iontophoretic Placebo Patch for Study of the Northstar Iontophoretic Lidocaine Patch.....	63
6.3.3.3	BDTS-00-16 Efficacy of the Northstar Iontophoretic Lidocaine Drug Delivery System for Anesthesia Prior to Treatment of Dermal Lesions by Laser	66
6.3.3.4	98NS 01-09 Blinded Prospective Evaluation of a Lidocaine Iontophoretic Delivery System	70
6.3.3.5	98NS 01-10 A Double-Blind Comparative Evaluation of the Northstar Iontophoretic System to Placebo in Pediatric Subjects	74
6.3.3.6	98NS 01-11 Blinded Prospective Evaluation of a Lidocaine Iontophoretic Delivery System	77
6.3.4	Uncontrolled Studies in Support of Efficacy	80
		80
		84
		85
		86
7	INTEGRATED REVIEW OF SAFETY.....	88
7.1	Brief Statement of Findings.....	88
7.2	Adequacy of Exposure and Safety Assessment.....	89
7.3	Methods for Review of Safety.....	91
7.4	Subject Demographics	91
7.5	Subject Disposition	93
7.6	Deaths	95
7.7	Non-Fatal Serious Adverse Events.....	95
7.8	Adverse Events Leading to Study Discontinuation.....	95
7.9	Overall Evaluation of Adverse Events	96
7.9.1	Approach to Eliciting Adverse Events in the Development Program	96
7.9.2	Appropriateness of Adverse Event Categorization and Preferred Terms.....	97
7.9.3	Analyses and Explorations.....	97
7.9.3.1	Incidence of Adverse Events in All Integrated Studies.....	97
7.9.3.2	Incidence of Treatment-Related Adverse Events in All Integrated Studies	101
7.9.3.3	Incidence of Adverse Events by Maximum Intensity in All Integrated Studies	103
7.9.3.4	Summary of Dermal Effects for Edema and Erythema in All Integrated Studies.....	103

7.9.3.5	Overall Incidence of Adverse Events	104
7.9.3.6	Studies of Repeat Application Effects and Dermal Irritation and Sensitization.....	105
7.9.3.7	Studies Not Included in the ISS Database	108
7.9.4	Laboratory Findings.....	110
7.9.4.1	Electrocardiograms.....	110
7.9.4.2	Vital Signs.....	111
7.9.4.3	Laboratory Findings	113
8	USE IN SPECIAL POPULATIONS	117
8.1	<i>Adequacy of By-Gender Investigation and Analyses.....</i>	117
8.2	<i>Elderly Population</i>	117
8.3	<i>Pediatric Population.....</i>	117
8.4	<i>Abuse Liability</i>	117
8.5	<i>120-Day Safety Update</i>	118
APPENDIX A		119
APPENDIX B		120

**APPEARS THIS WAY
ON ORIGINAL**

EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation on Approvability

Due to chemistry related deficiencies, the Northstar system will receive an approvable action. In addition, there are clinically related items outstanding (see Appendix A) which are not expected to affect the overall clinical findings, however are required to complete the review. These include safety reports from studies conducted under a — and retabulations of subject counts in the ISS and ISE, both of which were submitted too late in the review cycle for complete evaluation. Additionally, the sponsor will be asked to revise the presentation of adverse events associated with the Northstar system for labeling purposes. Based on the clinical information submitted and reviewed to date, I recommend approval of the Northstar system, but possibly with a more limited indication than proposed by the Sponsor. The Sponsor has demonstrated in multiple randomized, placebo-controlled, double-blind trials that the Northstar system both reduces sensation and diminishes the perception of pain compared to placebo when it is applied prior to venipuncture or intravenous cannulation. These trials support the claim of efficacy for use — on normal intact skin prior to venipuncture or intravenous cannulation. Only two trials are included in the NDA pertaining to use of the Northstar system —

— and the other failed to show a significant difference between the Northstar system and placebo in the pre-specified primary endpoint although the secondary endpoints did support efficacy. The safety profile of this product is similar to that of other iontophoretic devices approved for the administration of lidocaine and epinephrine with the exception of the incidence of papular rash that occurred overall in 7% of subjects treated with the Northstar system. The rash occurred more frequently in older children, aged 8 to 17 years old and resolved spontaneously, usually within 24 hours. There were no serious adverse events reported with the use of the Northstar system.

1.2 Recommended Phase IV Studies or Marketing Restrictions

1.2.1 Recommended Phase IV Studies

The sponsor had agreed in previous discussions with FDA to conduct trials of efficacy and safety in the pediatric population less than 5 years of age. At that time, it was agreed that such studies could be conducted as part of a Phase IV commitment.

Sensitization and irritation studies should be conducted as required for all dermally applied products. Human sensitization and irritation testing will be particularly relevant for this product due to the frequency with which papular rash occurred, especially in the pediatric population. The design of these studies should be made as consistent as possible with that recommended by the FDA Guidance for Industry, Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products.

1.2.2 Recommended Marketing Restrictions

There are no grounds for marketing restrictions of the Northstar system.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

The information submitted in this NDA pertains to the Northstar system, an iontophoretic device that provides dermal anesthesia by the transcutaneous delivery of lidocaine HCl in combination with epinephrine. The Northstar system is composed of a drug-filled patch connected to a direct current source (controller). Both the anode and cathode assemblies reside in a single patch. The patch anode contains the drug formulation, while the cathode acts as a return electrode during active treatment. The drug formulation in the anode is comprised of the local anesthetic, lidocaine HCl (100mg), and the vasoconstrictor, epinephrine (1.05mg), intended to lengthen the duration of anesthetic effect. The controller is an electronic system (including hardware and interconnect) designed to provide a preprogrammed direct current for transdermal iontophoretic drug delivery. A total charge of 17 mA•min, $[(3.4 \text{ mA} \cdot \text{min}/\text{cm}^2) \times 5 \text{ cm}^2]$ over a 10-minute interval, is provided.

The clinical development program consisted of studies conducted on three generations of a single integrated patch design in which the anode and cathode reservoirs were incorporated into single patch. The integrated designs, are referred to as Market Image Patch (MIP) I, II and III by the sponsor. Differences between the different generations of MIPs primarily involve upgrades to improve delivery, dosing, safety, ease of use and battery life. This NDA seeks approval for MIP III, the Northstar system.

The clinical trials were conducted under IND 48,365. MIPs I, II, and III and an earlier formulation, the — have been evaluated in 1438 subjects in 25 clinical studies. Nine of these studies evaluated the efficacy of the Northstar System (MIP III) in providing dermal analgesia (reduction of pain) for intravenous cannulation, venipuncture, and superficial dermatological procedures. —

—
—
— The devices were studied in adult and pediatric populations; no subjects were less than five years of age.

By agreement with FDA, the Sponsor has included data obtained from MIP II studies in the safety database. Safety data for 1143 subjects who received at least 1 application of the MIP III Northstar system or placebo in 4 placebo-controlled studies (N=661) and 6 open-label studies (N=482) were integrated and summarized in the Integrated Summary of Safety (ISS) database. The total number of subjects exposed to the MIP III was 1010, and the number exposed to the MIP II prototype was 168 yielding a total of 1178 subjects exposed to the Northstar system for the purposes of safety evaluation. Studies involving the MIP II and MIP III versions of the Northstar system utilized the to-be-marketed formulation of lidocaine 10%, epinephrine 0.1%, and a 10 minute iontophoretic period with a current density of 3.4 mA·min/cm².

2.2 Efficacy

Two pivotal studies were conducted in support of the indication of dermal analgesia for venipuncture or intravenous (IV) cannulation. Both of these studies were randomized, double blind, parallel-group, placebo-controlled, prospective, multicenter studies. The first study (BDTS-99-67) tested the Northstar system in adults (≥18 years of age), while the second study (BDTS-99-68) evaluated the 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%) and evaluated the pain associated with venipuncture or IV cannulation following the test treatment. Additional studies were conducted that also evaluated the efficacy of the Northstar system for topical dermal analgesia during the laser treatment of superficial skin lesions

In addition, 8 other Phase I studies were done using earlier prototypes of the Northstar system including one study that evaluated with the MIP I. The table below summarizes these trials.

Table 1. Summary of Efficacy Trials

Study	Phase	Type	Subjects ¹	MIP	Procedures
BDTS-99-67	III pivotal	controlled	270 adults	III	IV & venipuncture
BDTS-99-68	III pivotal	controlled	256 pediatric	III	IV & venipuncture
BDTS-00-16	III	controlled	66 mixed†	III	laser ablation of lesions
BDTS-99-24	I	controlled	20 adults	III	sensation testing
BDTS-99-25	I	controlled	32 adults	III	IV & venipuncture
98NS-01-09	I	controlled	44 adults	III	IV & venipuncture
98NS-01-10	II	controlled	48 pediatric	III	IV
98NS-01-11	I	controlled	48 adults	III	IV & venipuncture
BDTS-00-17	III	uncontrolled	88 adults	III	
95NS-01-01*	I	uncontrolled	12 adults	I	—
95NS-01-02	I	uncontrolled	3 adults	I	—
95NS-01-03A*	I	controlled	48 adults	I	cannulation
95NS-01-03B	I	controlled	60 adults	I	—

					cannulation
96NS01-04	I	controlled	63 adults	I	cannulation
96NS-01-05	I	controlled	36 adults	I	IV
96NS-01-06	I	controlled	62 adults	II	cannulation
96NS-01-07	I	controlled	80 adults	II	cannulation

[†]Efficacy evaluable subjects including those treated with placebo.

*Use of Good Clinical Practices not stated in study report.

†Included 10 pediatric patients and 56 adult patients.

The primary efficacy variables for evaluation of pain were Visual Analog Scale (VAS) scores for adults, and for children, the Nine-Face Interval Scale (NFIS). The scales were used to assess the pain associated with venipuncture, intravenous cannulation, and laser ablation of skin lesions approximately 10 minutes following treatment. To assess the depth of sensation, sensitivity testing with von Frey filaments was utilized.

Secondary endpoints included assessment of pain on removal of patch, using a logarithmic scale, parent/guardian assessment of child's pain using NFIS scores for children ages 5-11 years old, and VAS scores in addition to self-reported NFIS scores for children ages 12-17 years old. Clinician assessment of quality of anesthesia was used in studies in which superficial skin lesions were treated. Patient assessment of the sensation of the iontophoretic treatment was assessed using Hedonic VAS scores and Sensation Intensity Scale scores.

In both pivotal trials, treatment with the Northstar system prior to IV cannulation or venipuncture resulted in significantly lower pain assessment scores across age groups, gender and race. In the adult trial, the mean VAS scores, on a 10 cm scale, for the placebo arm and the Northstar arm were 2.53cm and 0.77cm, respectively (lower scores indicate less pain), and $p < 0.001$. In the pediatric study, an ordinal logistic regression of the NFIS scores indicated significantly less pain was experienced by Northstar-treated patients than placebo-treated patients, $p < 0.001$. In both of these trials, grouping patients at the extreme ends of the pain metrics allowed comparison of the numbers of patients who experienced little to no pain and those who felt severe pain. Using VAS scores of 0-3 and 7-10 and NFIS scores of A-C and G-I to represent these extremes, Northstar treatments consistently resulted in more patients experiencing little to no pain and fewer patients reporting severe pain than did placebo treatments. In the pediatric trial, parent/guardian scoring of pain and VAS scoring by the older children produced results consistent with the NFIS scores.

There were two studies evaluating efficacy of the Northstar system

The other trial was a placebo-controlled study of adult and pediatric patients undergoing laser ablation of superficial skin lesions. Although the primary endpoint, weighted VAS

Table 2. Summary of Trials Included in Integrated Summary of Safety Database

Protocol	Phase	n ¹	Placebo	Northstar
98NS-01-10	II	49	25	24
BDTS-00-10	I	12	0	12
BDTS-00-11	I	15	0	15
BDTS-00-16	III	67	33	34
BDTS-00-17	III	89	0	89
BDTS-00-40	I	43	0	43
BDTS-00-57	II	312	0	312
BDTS-99-56	I	13	0	13
BDTS-99-67	III	276	139	137
BDTS-99-68	III	272	136	136
Totals		1148	333	815

¹based on enrolled subjects

The number of subjects/patients exposed to the Northstar system (MIP III, to-be-marketed formulation) was 1010 when exposures not included in the ISS database are counted. Addition of subjects exposed to the MIP II patch, 168, which was agreed to by FDA, provided an overall number of subject exposures, 1178, that exceeded FDA's requirement of 1000. The demographics of the subjects included in the database are indicated in the table below. Age groups, (5 years of age and up), genders and races were adequately represented.

Table 3. Summary Demographics of the Subjects Included in the ISS Database

Demographic	N	Placebo	Northstar ¹
Age:			
5-7 years	105	41	64
8-11 years	162	60	102
12-17 years	163	62	101
18-64 years	553	146	407
≥65 years	163	24	139
Gender:			
male	460	141	319
female	686	192	494
Race:			
Caucasian	873	235	638
Black	105	46	59
Hispanic	101	43	58
Oriental	9	3	6

¹Data from subjects 002 and 004 in study BDTS-00-40 were not collected by Sponsor.

There were no deaths or serious adverse events reported for any trial during product development. As the designs of the clinical trials were such that treatments were completed in

one visit and the investigators applied the test products, compliance was assured. Monitoring of adverse events was performed by the investigators, the subjects, and in the case of pediatric subjects, the parents/guardians. Safety monitoring consisted primarily of visual assessment of patch application sites immediately upon patch removal, following the procedure, and 24 hours following the application. Loss to follow-up was not significant in any of the trials.

The most common adverse events included pain with the procedure and dermal reactions to the treatment including erythema, edema and papular rash. These were generally mild, typically resolved within 24 hours, and required no intervention. There were no adverse events that suggested serious toxic effects of the Northstar system. The comparison of

Repeat applications at different sites with 30-minute intervals between applications and a maximum of three applications have been shown to produce no toxicity related to systemic drug absorption. Studies of repeat applications at the same site and simultaneous application of multiple patches were not conducted.

2.4 Dosing

The dose of lidocaine and epinephrine are established based on the duration and magnitude of the current provided by the controller and the concentrations of the two products in the patch. Studies were conducted by the sponsor to optimize the analgesic effects while minimizing discomfort during iontophoresis, skin irritation and adverse events. Patches were evaluated using lidocaine: 0, 5 and 10%, epinephrine: 0, 0.01 and 0.1 mg, and iontophoretic charges of 0, 2.5, 3.4, and 4.2 mA·min/cm². From these studies, the optimal dose was determined to be a 10-minute treatment of 17.7 mA·min charge with 10% lidocaine and 0.1% epinephrine through an active anode 5 cm² in area. In theory, the delivered doses are 547 mcg of lidocaine and 6.2 mcg of epinephrine.

Repeat dosing safety studies were limited with a minimum of 30-minute intervals between Northstar applications and no more than three applications studied per subject. No studies were conducted to evaluate safety or efficacy for repeat applications at the same site or simultaneous applications of multiple patches.

2.5 Drug-Drug Interactions

No studies of drug-drug interaction potential were performed. Instead, the Sponsor cited the Xylocaine® label as it appears in the Physician Desk Reference. Specifically, the Sponsor proposes the following remarks to be placed in the PRECAUTIONS section of the product label.

The administration of local anesthetics containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine, which may shorten the duration of anesthesia. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

2.6 Special Populations

No clinically significant drug-demographic interactions were noted in the efficacy or safety analyses. The following assessments were made of the Phase II and III trials. Refer to Table 3 above for the numbers of subjects in different demographic groups.

Gender: A majority of subjects studied was female, but males represented approximately 40% of the total safety and efficacy databases. There were no apparent gender differences in safety or efficacy.

Race: Caucasians comprised the vast majority of subjects for the development trials. However, non-whites comprised nearly 20% of the safety and efficacy databases. Although the representation of individual racial groups was not adequate for a statistically meaningful comparison of safety and efficacy, there did not appear to be substantial differences in safety and efficacy among racial groups.

Elderly: At least 139 subjects aged 65 years and older were exposed to the Northstar system and they appeared to have a similar safety and efficacy profile compared to their younger counterparts.

Pediatrics: Over 250 pediatric subjects ages 5 to 17 years old were exposed to the Northstar system, with good representation of age subcategories. No differences were appreciable in either safety or efficacy between the pediatric and adult populations, or among the various pediatric subpopulations.

Renal and Hepatic Insufficiency: No studies were specifically designed to evaluate subjects with significant systemic disease, and no laboratory work was performed to screen subjects and thereby identify those with significant renal or hepatic impairment. Thus, subjects with either type of insufficiency were not identifiable and characterization of the effects, if any, of these conditions on either safety or efficacy could not be determined.

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PRIMARY CLINICAL REVIEW

1 INTRODUCTION AND BACKGROUND

1.1 Proposed Indications

The Sponsor's proposed indication for the Northstar system is

The Northstar system is an iontophoretic device designed to deliver lidocaine and epinephrine through the skin to provide analgesia for minimally invasive procedures. This is achieved by using a small electric current to deliver lidocaine and epinephrine into the skin in the vicinity of pain receptors and nerve endings. As both lidocaine and epinephrine are positively charged, they are delivered simultaneously from the circular drug reservoir.

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anesthetic action. Epinephrine has been shown to increase the depth and duration of anesthesia when co-administered with lidocaine presumably because of its vasoconstrictor activity, which decreases the rate of removal of lidocaine from the site of administration.

The rationale for iontophoretic delivery of a local anesthetic is that it avoids the pain associated with intradermal injection or infiltration and that it requires less time to achieve its effect compared to topically applied formulations.

A similar device, Iontocaine (NDA 020-530) also iontophoretically delivers lidocaine and epinephrine. Iontocaine uses a 40 mA•min charge dose with 2% lidocaine HCl and 0.01% epinephrine, whereas the Northstar system uses a 17 mA•min charge dose, 10% lidocaine HCl and 0.1% epinephrine.

1.2 Milestones in Product Development

The original IND for the Lidocaine Iontophoretic Delivery System was submitted by Becton-Dickinson (BD) on 14 July 1995 and was assigned IND number 48,365.

An End-of-Phase II (EOP2) meeting was held with the Division on September 16, 1999. The following agreements were reached regarding clinical issues.

- The FDA will address the need for a bioequivalence study to support post-approval changes after approval is granted.
- The FDA confirmed the need for reproductive toxicity, irritation, mutagenicity, chronic toxicity and carcinogenicity studies should the Sponsor choose to submit a 505(b)(1) application. If the Sponsor does not wish to conduct these studies, they will need to submit a 505(b)(2) application.
- The Sponsor will need to obtain additional data on blood lidocaine levels in their Phase III studies. It was suggested that such information could come from a study with at least 50 subjects where blood lidocaine levels were obtained at 0.5, 1.0 and 2.0 hours after application of the Northstar System.
- The Sponsor will conduct a Phase I study to analyze the depth of analgesia achieved. The FDA stated that in this study, all patients should be seen at 24 hours and that any patients who show signs of dermal burn, irritation, or other adverse events should be followed to resolution beyond 24 hours.
- The FDA indicated they would expect at least 1000 patients of diverse demography administered the MIPs or final patch formulation for an adequate safety database.
- The Sponsor was requested to provide written documentation to establish the comparability of the MIPII and MIPIII patches to satisfy this safety database requirement.
- The FDA noted that, since there are scale-down issues that have not been resolved, pediatric studies in children younger than five could be done as post-marketing studies.
- FDA requested the inclusion of geriatric patients in Phase III studies.
- The FDA noted that, before studying pediatric patients below age 2, —
- The Sponsor should analyze for burns in their Phase III studies and capture data on adhesiveness and burns on the CRFs.
- The Sponsor should not limit their studies to cannulation but should expand their Phase III plans to include other intended uses.
- Sponsor should consider their proposed labeling indication —
- Sponsor should study the local effects of repeated application to the same site, as well as the systemic effects of applications to multiple sites in a short period of time.
- Sponsor should develop a pediatric pharmacokinetic proposal.

A continuation of the EOP2 meeting of September 16, 1999 was held on February 17, 2000 at the request of the Sponsor. The following agreements were reached regarding clinical issues at that time.

- The FDA noted that repeat dose reproductive toxicity studies could be done by the subcutaneous route if there is a correlation of plasma concentrations with actual human exposure.
- The FDA noted that carcinogenicity studies are not required for local anesthetics intended for occasional use. Also, there need not be any mention of the carcinogenicity of — in labeling, as it is not relevant.
- Dr. McCormick informed the Sponsor that they could request a waiver from the reproductive toxicity studies if they had information to submit in the NDA to demonstrate undetectable

levels of lidocaine in the blood. This would require another pharmacokinetic study as the previous studies were flawed.

- FDA agreed that the overall Phase III clinical development plan is acceptable. FDA agreed that Sponsor could conduct studies in pediatric patients under the age of 5 as a Phase 4 commitment, allowing adequate time for the development of an appropriate patch for that pediatric population.
- It was agreed that it is not practical to monitor the actual current applied to patients.
- FDA agreed that safety data from studies using both the MIP2 and MIP3 patches could be combined with safety data from patients enrolled in the Phase III studies to establish the safety database for labeling purposes.

By letter of November 27, 2000, sponsorship of IND 48,365 was transferred from Becton Dickinson to Drug Delivery Technologies, Inc. (DDT).

By letter of March 27, 2001, Sponsor's name changed from Drug Delivery Technologies, Inc. to Vyteris, Inc.

A pre-NDA meeting was held with the Division on November 9, 2001. Agreements pertaining to clinical issues arrived at this meeting follow.

- FDA requested Sponsor to clearly define terms (like "burning sensation") in the NDA and use them consistently. Terms like "pain NOS" and "vasoconstriction" also need to be more clearly defined and details of the actual signs and symptoms need to be available for review.
- FDA requested that similar adverse events be grouped appropriately.
- FDA will require clinical safety data in humans (e.g. blood pressures, heart rate, and ECG) to evaluate the potential for systemic exposure to epinephrine.
- Sponsor should provide full documentation of the expected delivery of epinephrine from the device.
- The NDA should address special populations that might be particularly sensitive to epinephrine.
- FDA to make a determination on the applicability of the Combination Rule to this and other similar products which in past submissions had not been subject to the Combination Rule.
- Sponsor to provide a clear description of the differences between the prototype device and the to-be-marketed product.
- FDA requested Sponsor to address electrical safety issues and define appropriate sites as mentioned under "Application sites."
- FDA requested Sponsor to provide an understanding of the magnitude and method(s) of monitoring for burns as adverse events and to suggest ways that might burns from occurring.
- FDA agreed that if the NDA is a 505(b)(2) submission, reproductive toxicology studies can be waived and Sponsor could use available data in the public domain for safety of lidocaine and epinephrine.
- FDA reiterated the need for full toxicology profile, including reproductive toxicology studies for a 505(b)(1) submission.
- FDA noted that the Sponsor would get 3 years of exclusivity under a 505(b)(2) application if no similar product were approved first.

- FDA requested Sponsor to determine where their product fits in to the pediatric treatment arena and to request a waiver or deferral (i.e. < 5 years old) accordingly.
- FDA requested Sponsor to separate patients under 16 years of age by category in the ISS.

The Sponsor initially submitted NDA 021-504 on May 9, 2002 as a 505(b)(2) application referencing the FDA's previous findings of safety and efficacy for lidocaine (NDA 006-488) and citing the literature for information provided in the Nonclinical Pharmacology and Toxicology section of the NDA. The Agency had previously granted a waiver for bioavailability studies, and the Sponsor has certified that it is not violating any patent.

The application was withdrawn prior to the filing deadline after FDA discovered errors in data entry, uninterpretable formatting of data, and insufficient definition tables. The Sponsor resubmitted the NDA on September 25, 2002. FDA accepted that submission for filing.

1.3 Foreign Marketing

The Sponsor has not marketed the Northstar system in any foreign country and has no pending application for the product in any country. The product has never been approved or withdrawn from the market in any country.

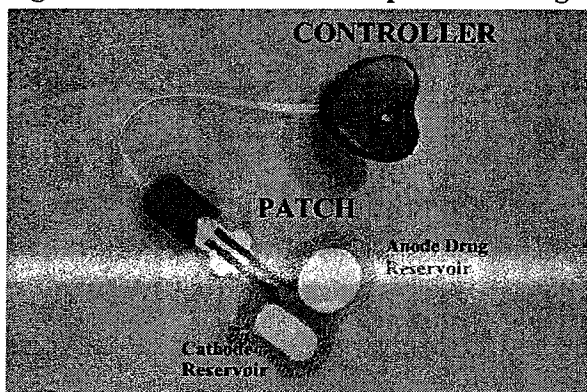
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2 SIGNIFICANT FINDINGS FROM CHEMISTRY AND ANIMAL PHARMACOLOGY AND TOXICOLOGY

2.1 Chemistry

The iontophoretic drug delivery system is a drug/device combination product consisting of a lidocaine iontophoretic patch and an electronic controller. A photograph of the patch and controller is shown in below. The lidocaine/epinephrine patch is the drug product referred to as the iontophoretic patch. The patch component is single use and disposable. The drug delivery system was developed and the IND submitted under the Project name Northstar.

Figure 1. Picture of the Iontophoretic Drug Delivery System (Northstar system) MIP III



The electronic controller is the device portion of the combination product and is designed to deliver a preprogrammed current to allow for the transfer of drug to the skin. The iontophoretic patch and the controller are electrically and mechanically connected as a system via an interconnect. The multi-use controller is submitted to the FDA under a separate 510(k) filed with the FDA.

The patch component consists of an electrode subassembly, which includes anode and cathode electrodes, backing film with peripheral adhesive, and flexible interconnect stiffener. In addition, it includes an anode hydrogel reservoir filled with drug formulation, cathode hydrogel reservoir filled with electrolyte formulation, anode and cathode transfer pads, and release cover. The iontophoretic patch is packaged in a foil/foil pouch, which provides a packaging and storage environment impervious to oxygen and light.

The lidocaine/epinephrine integrated iontophoretic patch is composed of anode and cathode pre-filled reservoirs that are connected to a direct current source (controller). The drugs are incorporated in the anode reservoir, which is polymeric polyvinylpyrrolidone (PVP). A salt-loaded (electrolyte) hydrogel serves as the cathode reservoir. The anesthetic drug, lidocaine, is transported in combination with a vasoconstrictor, epinephrine. The proposed role of epinephrine is to reduce the blood flow at the site, thereby inhibiting the rapid clearance of the

drug and prolonging the duration of anesthesia. The patch system consists of an integrated single patch where the anode and cathode electrode/reservoirs reside in a single unit. Electrical connection between the patch and the controller is made through a mating connector.

The peripheral adhesive surrounding the electrodes and reservoirs adhere the patch to the skin during the application. In addition, the peripheral adhesive helps the hydrogel reservoir maintain intimate contact with both the electrode and the skin throughout the application.

The Phase III integrated patch was developed from an earlier integrated version. The anode formulation was established during the Phase I clinical studies and has remained the same. The cathode formulations initially contained the cathode formulation was modified by adding monosodium phosphate

During the development, the hydrogel, anode drug solution, and the cathode electrolyte solution were challenged by an anti-microbial preservative effectiveness (APE) test to determine whether they were adequately preserved. The results indicated the cathode solution required preservation and a preservative was added. The anode solution and hydrogel met the APE test requirements.

The anode and cathode solutions were placed on stability to determine their shelf life. The solutions are reported to be stable for a minimum of

The integrated patch incorporates an anode and cathode transfer pad that covers the hydrogel reservoirs to provide a means for transferring the formulations dispensed during manufacturing to the hydrogel reservoirs. The manufacturing transfer efficiency has been found to be approximately 80%. The transfer pads are not part of the drug delivery system. The transfer pads are removed from the patch when the clinician removes the release cover to apply the patch. An overage is used in dosing the reservoirs to compensate for both the transfer efficiency and the loss of formulation due to back diffusion. In his review, Dr. Harapanhalli indicates that this is an acceptable procedure for transferring the formulations and that studies by the Sponsor demonstrated that drug loss by degradation was not an issue when the decrease in transferred product was first noted.

2.2 Pharmacology and Toxicology

This product uses an electrical current to facilitate the transdermal delivery of an anesthetic agent in order to achieve local anesthesia. Solutions of lidocaine and epinephrine are present in the anode portion of the patch and a saline solution is present in the cathode portion. Theoretically, during a single ten-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.

Both lidocaine and epinephrine are safe and effective therapeutic agents within therapeutic labeling and have a long history of use; their systemic and topical effects are well documented.

Based on these data and discussions with the FDA, the sponsor developed a preclinical testing plan that focused primarily on dermal effects (*i.e.*, local irritation or sensitization) following topical iontophoretic delivery of the test materials. (Information relative to the metabolism and pharmacology/toxicology of lidocaine is incorporated by cross reference to Xylocaine (lidocaine hydrochloride) NDA #6-488.) To support the safety of this new product, toxicity data have been collected on the product (*i.e.*, iontophoretic patches containing lidocaine and epinephrine), lidocaine alone, patches with lidocaine only, and extracts of the controller housing.

A series of nonclinical toxicology studies has been performed on the lidocaine/epinephrine iontophoretic patch (product), lidocaine alone, the iontophoretic patch with lidocaine alone, and extracts of the iontophoretic controller housing. Preliminary dermal irritation and guinea pig sensitization studies were conducted on prototype patches. In these studies, the patch generally produced minimal irritation. When an increased electrical current was used to stimulate iontophoresis, moderate irritation was reported. The preliminary sensitization studies were terminated early due to irritation. A follow-up study intended to identify possible reasons for the irritation suggested that epinephrine may have been responsible. Recently repeated dermal irritation and sensitization studies on the patch revealed that it was neither a dermal irritant nor a sensitizer. More recently, a 14-day repeat dose toxicity study was performed in rabbits using the current MIP-III patch design. The incidence and severity of dermal irritation was similar for both the patch and the placebo patch, but a higher incidence of scar-like areas was reported in the product-treated animals as compared to the placebo animals. Histopathology of the treatment site revealed an increased severity of reactive changes in the product group as compared to the controls.

For lidocaine alone, a skin irritation study was performed in rabbits. No irritation was observed in the animals. In addition, three genetic toxicity studies (Ames test, *in vitro* chromosomal aberration assay, *in vivo* mouse micronucleus test) have been conducted. All of these were negative for mutagenic activity.

A dermal irritation study was performed on a pH adjusted cathode (lowered to pH 4) version of a patch containing lidocaine alone. No evidence of skin irritation was reported.

In the controller extraction studies, an extract of the top and bottom housing was not cytotoxic in an *in vitro* assay using mouse fibroblasts. No evidence of irritation was observed in rabbits following exposure of the extract to intact and abraded skin sites, and no dermal sensitization was reported in guinea pigs.

Overall, the lidocaine- and epinephrine-containing iontophoretic patches produced no or minimal irritation following single doses and was not a sensitizer. Following repeat exposure, the patch produced a greater dermal response in rabbits (*i.e.*, scab-like areas, more severe reactive changes at pathological examination, focal degeneration of hair follicles) than the placebo patch. Studies on lidocaine alone revealed that the drug was neither irritating nor mutagenic. When a modified version of the patch was tested (with lidocaine alone), no skin irritation was produced in rabbits. Finally, controller housing extraction studies revealed no cytotoxicity *in vitro*, no skin irritation, and no skin sensitization. Based on these data, the Lidocaine Iontophoretic Drug Delivery System did not raise significant concerns for the proposed conditions of use in humans.

3 HUMAN PHARMACOKINETIC AND PHARMACODYNAMICS

3.1 Pharmacokinetic and Pharmacodynamic Studies

3.1.1 Pharmacokinetic Studies

Three studies were performed in human subjects to determine the extent of systemic absorption of lidocaine and one separate study was performed to determine the extent of systemic absorption of epinephrine following a standard iontophoretic drug delivery to the skin.

To measure plasma lidocaine concentrations two of these studies (BDTS-99-56) in adult subjects and BDTS-00-10 in pediatric subjects) used the MIP III delivery system, the subject of this NDA. Both studies were similarly designed with differences only in the age of the subject population (13 male/female adult subjects at ages 26-57 years in BDTS-99-56 and 12 male/female pediatric subjects at ages 6-15 years in BDTS-00-10). Both studies were single-center, randomized, repeat-application, open-label, Phase I studies with the objective to determine plasma concentrations of lidocaine following single and repeat treatment with the Northstar System.

In addition to the two above studies, a randomized, open-label, crossover, single-center study in 13 healthy male/female subjects, 19-44 years old, (98NS01-8) was performed with the utilization of the Northstar MIP II patch, a precursor to MIP III.

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

Since essentially all collected samples were below the limit of quantitation for lidocaine, four blood samples with measurable levels (<10 ng/mL) were determined to be contaminated, no pharmacokinetic parameters were calculated. Similarly, plasma levels of epinephrine were not appreciably different from endogenous levels; therefore, no pharmacokinetic parameters were calculated as no sampled concentration exceeded normal limits. These studies and their results are discussed in the Laboratory Findings subsection of the Review of Safety.

3.1.2 Summary of Drug Formulation Development

Formulation information was provided for all of the studies in which the integrated patch was used from MIP I through MIP III, the to-be-marketed product. These studies included all four of the bioavailability/pharmacokinetic studies, performed with MIP II and MIP III and all of the clinical studies (Phase I with MIP I and MIP II and Phase I, II and III with MIP III). The table below indicates the changes in development, identified by Specification Number, among the patches.

Table 4. Changes in Patch Formulation (table from HPKB section of NDA, p. 18)

Patch Mode	Specification No.	Formulation/Manufacturing Change	Reason for Change
MIP I	FS300048-2		First Integrated Patch
MIP II	FS300049	Physical re-design of MIP I patch.	Clinical findings showed that the MIP I design did not conform to subject's skin
MIP II	FS300050	Physical re-design of MIP I patch. Adjacent anode and cathode, Lidocaine 100mg, epinephrine, 1.0mg	Clinical findings showed that the MIP I design did not conform to subject's skin
MIP III	FS300058	Adjacent anode and cathode, Short tail, Decreased NaCl in anode solution, Added NaCl to hydrogel	
MIP III	FS300060	Mono sodium phosphate added to cathode solution; Transfer pads added; Amount of drug solution (lidocaine and epinephrine) dispensed increased by	; compensate for loss in transfer pad
MIP III	FS300063	Preservative added to cathode solution	Preserve the cathode solution as a component
MIP III	SP300017	None*	None*

*The Sponsor stated the following in reference to this MIP. After the transfer pad was incorporated, 100 mg of lidocaine HCl and 1.0 mg of epinephrine free base are dispensed during manufacturing. 1.0 mg of the solution transfers from the transfer pad to the hydrogel. Therefore, 99 mg lidocaine and 0.9 mg of epinephrine free base are transferred into the hydrogel. The label claim should have been 100 mg lidocaine and 1.05 mg of epinephrine for those patches containing the transfer pad.

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4 DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

The primary source of data for this NDA review was the clinical trial program of the Sponsor as reported in the NDA and as supplemented by additional submissions received during the review period. Relevant literature and the assessments of other reviewers were also considered in the final evaluation of safety and efficacy. Data submitted to a — were received on July 18, 2003 and could not be reviewed during this cycle.

4.2 Overview of Clinical Trials

The table below identifies and describes the studies, which formed the basis for this review. Some studies may appear under more than one heading.

Clinical studies of the iontophoretic delivery of lidocaine in combination with epinephrine have been performed in —

— These studies involved an early version of the iontophoretic patch, i.e., they preceded the development of the Northstar system in the United States, and were not included in the NDA. The Sponsor reports summarizing the safety data from these studies on July 18, 2003, too late for full evaluation and inclusion in this review.

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Table 5. Listing of Studies Reviewed for Safety and Efficacy

Study Type	Study Number	Phase of Development	Patch Version(s) Studied
Pharmacokinetics:	BDTS 99-56	I	III
	BDTS 00-10	I	III
	Vyteris-01-01	I	III
	98NS 01-08	I	II
Clinical Pharmacology:	BDTS 00-40	I	III
	Vyteris-01-01	I	III
Controlled Clinical Trials for MIP III:	BDTS 99-67	III	III
	BDTS-99-24	I	III
	BDTS-99-25	I	III
	98NS 01-11	I	III
	98NS 01-09	I	III
	BDTS-00-16	III	III
	BDTS-99-68	III	III
	98NS01-10	II	III
	BDTS 00-17	III	III
Uncontrolled Clinical Trials for MIP III:	BDTS 00-11	I	III
	BDTS 00-57	II	III
	BDTS 99-73	I	III
	BDTS 99-73	I	III
Clinical Trials for MIP I and II and III:	98NS 01-07	I	II
	97NS 01-06	I	II
	96NS 01-05	I	I
	96NS 01-04	I	I
	95NS 01-03B	I	I
	95NS 01-03A	I	I
	95NS 01-01	I	I
	95NS 01-02	I	I
	95NS 01-02	I	I

4.3 Postmarketing Experience

The Northstar system is not marketed in the United States or foreign countries. There is however, safety information available on a similar product, Iontocaine® which iontophoretically delivers lidocaine and epinephrine and is marketed in the United States. Iontocaine uses different doses of lidocaine, epinephrine and charge, but would be expected to have a similar safety profile. According to the package insert, adverse events occurring with Iontocaine® include urticarial reaction (approximately 6%) primarily under the dispersive electrode, rash (1%) and burning sensation (5%) under the dispersive electrode, paresthesia (3%), and taste perversion (1%). Abrasion, application site reaction, ecchymosis, petechia, hypesthesia, dizziness, pain, postural dyspnea, and redness lasting greater than 24 hours occurred in <1% of

the subjects. In all but one instance, these reactions did not interfere with the iontophoresis treatments.

The Iontocaine® package insert also stated that animal studies showed that a single application of the product can cause erythema and edema, and that multiple applications could cause acanthosis, hyperkeratosis, inflammatory response, hemorrhage and/or necrosis involving only epidermis and papillary dermis. These lesions resolved after one week.

4.4 Literature Review

The Sponsor has conducted a review of the literature related to the pharmacokinetics and pharmacodynamics of epinephrine, iontophoresis, Draize scoring, chemical analysis techniques and statistical analysis of datasets. Copies of the articles utilized in product development were included with the NDA.

Review of the literature provided and that found independently of the Sponsor raised no concerns regarding the safety or efficacy of lidocaine and epinephrine when used as proposed in the Northstar system. Furthermore, the literature was supportive of the proposed use of these drugs in terms of the doses and indications.

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5 CLINICAL REVIEW METHODS AND DATA INTEGRITY

5.1 Conduct of Review

The review began by determining that all applicable items of the clinical section were included and that the NDA was suitable for filing. During the review for filability of the initial submission, it was noted that the data tables included values that were several orders of magnitude out of range compared with other values obtained under the same circumstances and in a similar manner. Also noted at that time were presentation of time values that were preceded by inappropriate punctuation marks rendering them suspect for accuracy and usefulness in further analysis as well as data variables that were incorrectly defined. In addition, the presentation of data was not consistent with the Guidance for Industry in terms of textual descriptors for data such as subject gender or race, and type of treatment administered. After discussion with the Sponsor, Vyster elected to withdraw this initial NDA submission. A revised NDA was submitted four months later with the deficiencies remedied. The revised NDA was filed by the Agency.

Data from the two pivotal trials, all of the other controlled-clinical trials and those uncontrolled trials that contributed to the findings of efficacy were reviewed in detail. This included review of trials using earlier versions of the Northstar system when appropriate. The safety review consisted of a review of the Integrated Summary of Safety (ISS), verification and additional analyses of the ISS database, review of the case report forms and case report tabulations, and review of the safety data of those studies not included in the ISS database but which utilized the MIP II or MIP III versions of the Northstar system.

At times during the review process, questions regarding various aspects of the Sponsor's data gathering and analysis or of the data itself were forwarded to the sponsor. Copies of these requests to the Sponsor are included in Appendix B of this review.

5.2 Materials Consulted in Review

The table below contains the items provided by the Sponsor and generated by the FDA that were utilized in the course of this review.

Table 6. Items Consulted for Review

Item	Date	Description
NDA 21-504	5/9/2002	initial NDA submission – FDA refused to file
NDA 21-504 (N-000-XP)	6/4/2002	patent information
NDA 21-504 (N-000-XP)	6/21/2002	patent information
NDA 21-504 (N-000-RS)	9/25/2002	revised NDA submission – FDA filed
NDA 21-504 (N-000-BM)	6/13/2003	response to request for additional clinical information
NDA 21-504 (N-000-BZ)	6/13/2003	response to request for clarification of clinical study data table values
NDA 21-504 CRT	6/20/2003	revised CRT in response to FDA request

Item	Date	Description
NDA 21-504 (N-000-BM)	6/24/2003	response to request for clarification of differences between patch systems
Division file for IND	7/14/1995 – 7/28/2000	Division reviews, minutes of meetings with Sponsor, correspondence with Sponsor

The following amendments to the NDA were not submitted in time for full review during this cycle: N-000-BZ (06/28/03), N-000-BZ (07/15/03), N-000-BM (07/18/03), and two N-000-C (07/18/03)s.

5.3 Evaluation of Data Quality and Integrity

The original NDA submission was evaluated for data integrity and quality by retabulation of the data to verify results reported in the Integrated Summary of Efficacy and the Integrated Summary of Safety and evaluation of the datasets for reviewability, completeness, consistency, and coherence. In this process, the following were observed.

1. Coded columns of data were not accompanied by corresponding columns of full term descriptors, e.g., AEGRADCD had undefined codes 1-3 and should have had a corresponding column with “mild,” “moderate” and “severe.”
2. Symbols were used in the same data column to describe two different things, e.g., DRZNACD contained “. = Burn Assess or Missing.”
3. Some data were not internally consistent suggesting that the final data sets were not fully QC tested. For example,
 - Patient #2237 was listed as having an ongoing AE (AEONGCD=1), but also had a time of resolution listed (AEETMS=19:00).
 - AERELCD missing data patient number (#1109) does not match the number listed in the data variable codes (#2201).
4. Spaces in data tables were left blank making it ambiguous as to whether there was no data to report or data entry was overlooked.

These issues, with others, were brought to the Sponsor’s attention and resolved in the subsequent submission. In the revised submission, integrity was evaluated by using the data tables to regenerate summary reports and key results from the trials used for determination of efficacy. Summary tables of the ISS were generated to verify demographic data reports and adverse event reporting. An accounting was made of all subjects who were randomized in trials and of all subjects who received the drug product in any trial. Comparisons were made of case report tabulations and case report forms for subjects with adverse events who were discontinued from studies.

5.4 Conduct in Accordance with Accepted Ethical Standards

The initial 3 studies conducted in human volunteers were performed by ———. These studies were neither submitted for review nor described by the Sponsor in the NDA. Their discovery came from review of the study reports of the early clinical trials. The sponsor has been advised to submit the final study reports, data tables and appropriate CRFs. Their submission was pending at the time this review was completed. Evaluation of those studies will be amended to this review when they have been received.

With the exceptions of trials 95NS-01-01 and 95NS-01-03A, all studies reported that they were conducted in accordance with the ethical principles included in the "Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964; and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; the 35th WMA General Assembly, Venice, Italy, October 1983; the 41st WMA General Assembly, Hong Kong, September 1989; and in the later trials, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Similarly, the same trials reported being conducted according to the United States (US) Food and Drug Administration (FDA) Good Clinical Practice (GCP) guidelines for the ethical conduct of clinical studies.

5.5 Evaluation of Financial Disclosure

To comply with 21CFR §54.4, Certification and Disclosure Requirements, the Sponsor submitted certification on the financial interest and arrangements of the clinical investigators who enrolled subjects into the covered clinical studies of the Northstar system.

In a disclosure statement, the Sponsor indicated that investigators who enrolled subjects into the covered clinical studies who were full-time employees of Becton Dickinson & Company at the time of the clinical investigation were compensated by salary and other agreements as a part of their employment. Financial disclosures were not signed by those employees. The trials in which these investigators were involved included 98NS-01-09, 98NS-01-11, and BDTS-99-25.

Two investigators involved with protocol ——— did not provide certification despite the Sponsor's due diligence to secure same. It was unknown if either had disclosable information.

All other investigators had no disclosable information.

The three studies cited above, in which investigators were employees of Becton Dickinson & Company, were all Phase I trials. It is not expected that the investigators' status in the company at that point in product development would have undue influence on study conduct or outcome.

6 REVIEW OF EFFICACY

6.1 Brief Statement of Conclusions

Based upon the data submitted from the pharmacokinetic and clinical trials, the following conclusions were drawn regarding the Northstar system's development and proposed label claims.

1. The sponsor has satisfied the requirements of the combination rule by demonstrating improved efficacy of iontophoretically applied lidocaine and epinephrine over that of iontophoretically applied lidocaine or epinephrine alone and over that of lidocaine and epinephrine applied without current.
2. The sponsor has demonstrated that the use of a patch system containing only epinephrine is not significantly different, in terms of anesthesia, than a placebo patch containing neither epinephrine nor lidocaine.
3. The Sponsor has demonstrated that the Northstar system diminishes sensation more than placebo.
4. The Sponsor has demonstrated that the Northstar system significantly reduces the level of pain associated with venipuncture and intravenous cannulation compared to placebo when applied to relatively hairless and normal appearing skin.
5. The Sponsor has not adequately demonstrated that the Northstar system is significantly better than placebo in reducing the level of pain associated with
✓ laser ablation of superficial skin lesions. Only one controlled trial was submitted which did not achieve significant difference from placebo for the primary endpoint, but whose secondary endpoints were supportive of efficacy.

6.2 Approach to Review of Efficacy

The table below provides a list of studies reviewed to reach the efficacy conclusions outlined above. The first two studies listed were the pivotal trials and were reviewed in detail. The others have abbreviated reviews. Also briefly reviewed were the trials conducted using the system and the MIP I patch.

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Table 7. Studies Reviewed for Contributions Towards Efficacy Findings

Study	Contribution to Efficacy	Control Status	Phase	MIP
BDTS-99-67	analgesia; combination rule* (lidocaine)	controlled	III	III
BDTS-99-68	analgesia; combination rule (lidocaine)	controlled	III	III
98NS-01-07	analgesia; combination rule (epinephrine)	controlled	I	II
98NS-01-09	analgesia; combination rule (current)	controlled	I	II & III
98NS-01-10	analgesia; combination rule (current)	controlled	II	III
98NS-01-11	analgesia; combination rule (current)	controlled	I	III
BDTS-00-16	analgesia for dermal procedures; combination rule (lidocaine)	controlled	III	III
BDTS-99-24	depth of pain sensation, combination rule (lidocaine)	controlled	I	III
BDTS-99-25	analgesia; combination rule (lidocaine & current); proof of concept for placebo patch	controlled	I	III
BDTS-00-17		uncontrolled	III	III

* Component listed in parentheses is the one that was included in the test product and excluded, or used in reduced amounts, in the placebo formulation.

6.3 Review of individual, controlled studies contributing to conclusions of efficacy

6.3.1 Study BDTS-99-67: A Double-blind Evaluation of the Northstar Lidocaine Iontophoretic Drug Delivery System in Adult Subjects

6.3.1.1 Overall Design and Summary of Findings

This study was a multicenter, randomized, placebo-controlled, double-blind, parallel group trial assessing the pain associated with either venipuncture or insertion of an intravenous cannula (IV) in adults. The placebo consisted of Northstar system in which the lidocaine hydrochloride was replaced with normal saline solution. Epinephrine was contained in both the Northstar system and the placebo. Pain was assessed immediately after the procedure using a Visual Analog Scale (VAS).

A total of 276 subjects were randomized and 270 subjects completed the study. The subjects who were treated with the Northstar system experienced significantly less pain than the recipients of the placebo ($p < 0.001$). More Northstar treated subjects reported little to no pain, a VAS score of 0 or 1 out of 10, than did placebo; 82.2% versus 32.4%, respectively. When analyzed according to gender, race or age, the results were similar in all subpopulations, which included male and female, white and black, and younger than 65 years and 65 years of age or older.

6.3.1.2 Study Plan

The original version of this protocol was dated September 28, 2000. Two amendments were made, amendment 1 was dated December 13, 2000 and amendment 2 which was dated February 28, 2001. The first subject was entered on December 4, 2000 and the last subject completed the study on March 2, 2001. Revisions to the protocol were such that no significant impact was had on the conduct of the study, results obtained or conclusions drawn.

Source: NDA submission, Clinical Study Report for Protocol No.: BDTS-99-67 pp. 1, 91

6.3.1.3 Objectives

The protocol-specified objective of the study was:

“to demonstrate the safety and efficacy of the Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar) compared to a placebo system when used for local dermal anesthesia on intact skin.”

6.3.1.4 Design

In this clinical study, the Northstar system was to be tested for its ability to decrease the pain felt by subjects undergoing a routine venipuncture for phlebotomy or intravenous (IV) cannulation. The study was to compare the Northstar system, administering 10% lidocaine and 0.1% epinephrine, with an otherwise identical placebo system in which lidocaine was replaced with sodium chloride (NaCl). The anode of the placebo patch contained 1.05 mg epinephrine per patch, as did the active patch.

The protocol was to be designed as a randomized, double-blind, parallel-group, placebo-controlled, prospective, multicenter clinical study. Each subject was to receive a single treatment with either a Northstar or a placebo system approximately 15 minutes before a scheduled venipuncture or intravenous (IV) cannulation procedure. Skin at the application site was to be examined for dermal reactions immediately following removal of the patch system. Subjects were to be evaluated for the pain they experienced from the venipuncture/IV cannulation procedure using a Visual Analog Scale (VAS). Each subject was to return to the center 24 ± 4 hours later so that the treatment area could be assessed again for dermal reactions.

6.3.1.5 Primary Efficacy Variable

The primary efficacy variable was the level of pain experienced from the venipuncture/IV cannulation procedure as measured using a 10-cm Visual Analog Scale (VAS). Pain assessment scores ranged from 0 to 10 with 0 representing “no pain” and 10 representing “severe Pain.” There were no other efficacy variables evaluated in this protocol.

6.3.1.6 Population

Patients were to be selected from adults, both inpatients and outpatients, presenting for routine venipuncture or intravenous cannulation. There was to be no upper age limit on patient inclusion. The following criteria were to be used in patient selection.

Inclusion Criteria:

- male or female 18 years of age or older
- in the opinion of the investigator, is medically stable
- willing to complete all study procedures
- able to provide informed consent
- available for the study days
- the expected duration for IV cannulation is 12 hours or less

Exclusion Criteria:

- obvious skin imperfections (moles, marks, bruises, cuts, abrasions, discolorations, or abnormalities) on the test site
- excessive hair, which in the opinion of the investigator, will interfere with patch adhesion (clipping or shaving of hair is not permitted)
- known sensitivity to amide anesthetics and/or epinephrine
- pregnant or lactating females
- has had a needle stick within 24 hours prior to the baseline visit (Visit 1)
- current or history of dermal conditions that contraindicate use of iontophoretic treatment, such as skin allergy or hypersensitivity to metals and/or adhesives, electrodes and other components of the patch, active dermatitis, petechial hemorrhagic areas, and/or easy bruising
- current or history of systemic conditions that contraindicate use of iontophoretic treatment, such as any systemic vasculitis
- current or history of medical condition that would contraindicate treatment with the product, such as neurological disorders, psychological disorders, psychiatric disorders, or other conditions which, in the opinion of the Investigator, would place the patient at risk or has the potential to confound interpretation of the study results
- presence of implanted or externally mounted electrical or electronic medical devices (i.e., pacemakers, transcutaneous electrical nerve stimulators [TENS] units, etc.)
- history of fainting, arrhythmia or irregular pulse
- treatment with iontophoresis or participation in venipuncture/IV cannulation, investigational product, or patch testing studies within 30 days prior to this study
- use of any medication having an analgesic effect (such as aspirin and other non-steroidal anti-inflammatory drugs) is not allowed 48 hours before study treatment and until all pain assessments are completed. Regular strength, over-the-counter Tylenol may be taken at the labeled doses up to 24 hours before treatment. Chronic aspirin use for cardiovascular or cerebrovascular prophylaxis is permitted, if the average daily dose does not exceed 325 mg (1 adult regular strength tablet).
- use of systemic or topical corticosteroids, not including nasal or inhaled corticosteroids, within 3 weeks before treatment.

Participants could be withdrawn from the study at their own request for any reason, or at the discretion of the principal investigator, or for any of the following reasons:

- There was an indication that the patient had an allergic reaction to Northstar (e.g. hives, itching, anaphylaxis, low blood pressure, bronchospasm, or edema)
- There was an indication of toxicity from the test article (e.g. numbness of the tongue, lightheadedness, visual disturbance, muscular twitching, or convulsion)
- Incomplete delivery of Northstar treatment, either active or placebo, as indicated by the incomplete delivery light being illuminated on controller during the iontophoretic delivery cycle or if manual discontinuation occurs for any other reason. In instances of incomplete delivery, patches were to be examined to determine the effectiveness of the adhesion.
- Patient was non-compliant or uncooperative
- Patient was lost to follow-up
- Patient was discovered to be a protocol violator
- It was determined by the investigator to be in the patient's best interest
- Administrative reasons, including but not limited to:
 - Failure to return for follow-up visits.
 - Termination of the trial by the sponsor.

6.3.1.7 Methods and Procedures

The table below (taken from Table 2 from the Protocol BDTS-99-67 Final Study Report), provides the details of which data were to be collected according to the study phase. Following initial evaluation, randomization, and instruction on assessing pain using the Visual Analog Scale (VAS), the patch was to be applied to the test site (Visit 1). The site was to be cleaned with alcohol and allowed to dry. Test sites were not to be shaved or clipped of excess hair, and were to be marked with an indelible marker to facilitate locating the anode and cathode sites at follow-up (Visit 2). The patch was to be applied so that the anode was over the vein, and if needed, it was to be secured with paper tape, , etc. to ensure complete contact with the skin. The patch was then to be attached to the controller, which was to deliver a 10-minute treatment. After treatment, before removal, the patch was to be examined for the effectiveness of the adhesive. The patch was then to be removed. Within 10 minutes of removal, but before venipuncture or IV cannulation, the treatment site was to be evaluated for erythema and edema using the Draize scale. Approximately 10 minutes following treatment, venipuncture or intravenous cannulation was to be performed, and 10 minutes later, VAS pain scores were to be obtained. The site was to be evaluated again at 24 hours after the start of treatment. If skin at the region of Northstar System application was observed to have a more significant reaction than would ordinarily be expected after the venipuncture/IV cannulation (e.g. if Draize score > 3 for either erythema or edema and that was not explained by the scope of the procedure), the patient was to be followed at 24-hour intervals until the investigator determined that the condition no longer warranted medical intervention.

Adverse events of erythema and edema at the site of patch application were to be collected in the CRF using the Draize Score (scores from 0 to 4) criteria. Erythema and edema were to be reported as AEs only when the Draize Score was recorded as 4.

Table 8. Study Schedule (Table 2 from BDTS-99-67 Final Study Report, p.111)

Procedures	Visit 1 (Day 1)			Visit 2 (Day 2)
	Baseline	Post -patch	Post-Venipuncture/ IV Cannulation	
Obtain Informed Consent	X			
Verify Inclusion/Exclusion	X			
Demography	X			
Vital signs (heart rate, oral or tympanic temperature, respirations, blood pressure, height, weight)	X		X ^a	
Medical history	X			
Urine pregnancy test	X ^b			
Examine test site	X			
Venipuncture/IV Cannulation		X		
VAS (Pain assessment)			X	
Draize Scale (Visual Scoring of Dermal Reaction)		X		X
Concomitant Medication Assessment	X ^c			X
Adverse Event Assessment		X	X	X

^aPost-venipuncture/IV cannulation vital signs include blood pressure, heart rate, and respirations.

^bFor females of childbearing potential.

^cConcomitant medication assessment should include all medications used 30 days before Visit 1.

Patients who had a Draize score of 4 at any timepoint were to be further evaluated by the investigator to assess whether they had received a 'burn' from exposure to the test article. As part of the assessment of burns, all patches were to be examined before removal to determine the effectiveness of the adhesion. Adhesion was to be scored according to the following table (taken from Table 3 of the Protocol BDTS-99-67 Final Study Report).

Table 9. Adhesion Scoring (Table 3 from BDTS-99-67 Final Study Report, p. 24)

Description	Score
90-100% adhered (essentially no lift off of the skin)	0
75% - < 90% adhered (some edges only lifting off of the skin)	1
50% - 75% adhered (less than half of the system lifting off the skin)	2
< 50% adhered but not detached (more than half of the system lifting off the skin without falling off)	3
Patch detached (patch completely off the skin)	4

All events which were determined to be a burn related to the test article were to be investigated by the Sponsor to determine the mode of injury: electrical contact, pH change, loss of (anode) contact, or other. As part of the investigation, the test articles associated with identified burns were to be returned to the Sponsor for evaluation.

6.3.1.8 Analysis Plan

The efficacy analysis was to be based on the ITT population, defined as all subjects who received the study treatment and evaluated their pain after a procedure. All randomized subjects who received the study treatment were to be included for the safety analysis. Baseline was defined as the last measurement before the study treatment. All data collected on the CRFs were to be presented in subject data listings by treatment and subject. Summaries of subject disposition, demographic and baseline characteristics, concomitant medications, VAS scores (primary efficacy), Draize scores, AEs, and vital signs were to be tabulated by treatment.

6.3.1.8.1 Analysis of Efficacy

Using a 10-cm VAS, subjects were to assess the level of pain experienced immediately after the venipuncture/ IV cannulation. The VAS scores were to be analyzed using the following analysis of variance (ANOVA) model:

$$\text{VAS score} = \text{Center} + \text{Procedure} + \text{Treatment} + \text{Error}$$

The Sponsor states that the interaction term of center by treatment and procedure by treatment were removed from the model because they were not significant at the 0.10 significance level. All subjects who completed the first visit and had pain evaluated after the procedure were to be included in the efficacy-evaluable population and their data were to be analyzed.

6.3.1.8.2 Determination of Sample Size

A sample size of 125 subjects per group was needed 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. Approximately 275 subjects were to be enrolled at approximately six investigative sites to achieve at least 250 evaluable subjects. Approximately equal numbers of subjects were to be enrolled at each site with no more than 60 subjects at any site. Approximately equal numbers of each procedure (venipuncture or IV cannulation) were to be performed at each site, and neither procedure was to comprise <40% of the enrollment for that investigative site.

In order to achieve study enrollment, centers that were able to enroll additional subjects were allowed to do so during the course of the trial. Enrollment at two centers (= 75; = 63) exceeded the limit of 60 subjects, while the remaining sites enrolled less than 60 subjects.

This was noted as a protocol deviation, but was approved by — because it would not affect the final statistical analysis.

A completed subject was one who had both Visit 1 and Visit 2 evaluations. Subjects who did not return for Visit 2 evaluations were to be replaced after consultation with the Sponsor or the Sponsor's representative.

6.3.1.9 Protocol Amendments

There were two amendments to the study protocol dated 7 December 2000 and 28 February 2001. The following major changes were made:

Changes Effective 7 December 2000:

- The Sponsor's name was updated to Drug Delivery Technologies, Inc., from Becton Dickinson Transdermal Systems
- To ensure appropriate randomization within each procedure, the randomization was split so that subjects undergoing venipuncture were assigned subject numbers in the 1000 series and those undergoing IV cannulation were assigned numbers in the 2000 series
- More detailed information was added to the Draft Product Labeling section
- The exclusion criteria were modified as follows:
 - excluded subjects who had a needle stick within the 24 hours prior to the baseline visit (Visit 1)
 - excluded subjects who participated in IV cannulation studies within the 30 days prior to the study
 - disallowed the use of medications with analgesic effect within the 48 hours prior to the study treatment and until all pain assessments were completed
 - allowed nasal or inhaled corticosteroids
- A clarification was added that temperature could be measured orally or tympanically
- A concomitant medication assessment was added at Visit 2
- Clarification was added to the discussion of Draize scoring regarding follow-up for dermal effects
- Clarification was added to specify that burns related to the test article would be investigated by the Sponsor
- Sites were instructed to return the used patch to Vyteris, Inc., in the event of an AE or incomplete drug delivery
- The statistical analyses were amended to include an ordinal logistic regression of Draize scores to be used to compare score distributions between the dermal effects of the two groups. Center, procedure, and treatment were included as factors in the model. A Cochran-Mantel-Haenszel mean score test, stratified by center, was to be performed as a secondary analysis
- The sample size assumptions were revised to detect a difference in the 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
- Minor additions were made to the instructions for use of the Northstar system

Changes Effective 28 February 2001:

- The Sponsor's name was updated to Vyteris, Inc., from Drug Delivery Technologies (formerly Becton Dickinson Transdermal Systems)
- A statement was added that all subjects who completed the first visit would be included in the efficacy evaluable population and analyzed

None of these amendments were expected to significantly affect the results of the study.

6.3.1.10 Study Conduct

The study was conducted as planned. The Sponsor notes that the study was undertaken only after full approval of the clinical study protocol was obtained from an Institutional Review Board. The study was conducted in accordance with both Good Clinical Practice (GCP) Guidelines and the ethical principles included in the "Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; the 35th WMA General Assembly, Venice, Italy, October 1983; the 41st WMA General Assembly, Hong Kong, September 1989; the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

The Sponsor contracted with an independent organization, _____, to monitor this study and provide data quality assurance. To this end, recorded data, where available, were monitored to verify accuracy compared with the CRFs. Upon closeout of the study, a full audit of the data was performed.

A database was prepared from data entered on the CRFs. Data security was ensured through password protection and regular backups of the data. Upon completion of the study and verification of the data, an audit of at least 10% of the database was conducted. Upon completion of the audit, the database was locked to prevent any additional changes. A copy of the locked database was provided to the _____ for statistical analysis.

6.3.1.10.1 Patient Disposition

Five investigators randomized a total of 276 subjects into the study: 137 subjects who received the Northstar system (Northstar) and 139 subjects who received the placebo system (placebo). Two subjects who received the Northstar system were enrolled into the study twice without the approval of the Sponsor. The subjects (Nos. 2013 and 1015) were assigned new subject numbers when they re-enrolled (Nos. 1125 and 2017, respectively); therefore, their data were considered as four individual subjects instead of two. Subject disposition is presented in Table 4. A total of 134 subjects (97.8%) in the Northstar group and 136 subjects (97.8%) in the placebo group completed the study.

Six subjects prematurely discontinued from the study; three subjects (2.2%) in each group. In the Northstar group, 1 subject (0.7%) was lost to follow-up, and 2 subjects (1.5%) discontinued due to “other” reasons, specifically, that the patch was inadvertently removed by the anesthesiologist prior to the completion of treatment. In the placebo group, three subjects (2.2%) discontinued due to technical failure. No subjects discontinued from the study due to AEs.

Table 10. Subject Disposition (Table 4 from BDTS-99-67 Final Study Report, p. 34)

Subject Status	Northstar	Placebo
	n (%)	n (%)
Randomized	137 (100.0)	139 (100.0)
Completed	134 (97.8)	136 (97.8)
Prematurely Discontinued Study	3 (2.2)	3 (2.2)
Technical Failure	0	3 (2.2)
Adverse Event	0	0
Consent Withdrawn/Refused Further Treatment	0	0
Death	0	0
Protocol Violation	0	0
Lost to Follow-Up	1 (0.7)	0
Other	2 (1.5)	0

The following table lists the protocol violations for this study. It was noted that the violations occurred in subjects who were randomized and completed the study. The violations occurring in subjects receiving treatment with the Northstar system would not likely affect the efficacy results, however, the two subjects who used corticosteroids within three weeks prior to treatment may have had Draize scores that were decreased by the steroids if the dose was sufficiently large or recently administered to still have a significant effect. The use of analgesics by the placebo treated subjects may have resulted in lower VAS scores if their treatment had been excessive for the indication and/or administered too close to their participation in the study. Overall, it was not expected that these violations would have significantly affected either the efficacy or the safety results of the study.

Table 11. Protocol Violations (Table 5 from BDTS-99-67 Final Study Report, p. 34)

Subject	Treatment	Violation	Exclusion No.
0003/1008	Northstar	Subject used systemic or topical corticosteroids within 3 weeks before treatment.	13
0005/2014	Northstar	Subject used systemic or topical corticosteroids within 3 weeks before treatment.	13
0004/2100	Northstar	Subject participated in an investigational product study within 30 days before this study.	11
0004/1101	Placebo	Subject had a pacemaker, had history of atrial fibrillation, and took analgesics within 48 hours of Visit 1.	9, 10, and 12
0002/1131	Placebo	Subject participated in an investigational product study within 30 days before this study.	11
0004/1141	Placebo	Subject took methadone.	12

6.3.1.11 Demographics/Group Comparability

The table below presents a summary of the demographic and baseline characteristics of all randomized subjects. There were significantly more female subjects, Caucasian subjects and subjects under age 65 years. The distribution of subjects between Northstar and Placebo arms was similar in terms of subjects' gender, age, race, height, weight, and procedure.

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Table 12. Demographics and Characteristics (Table 6 from BDTS-99-67 Final Study Report, p. 36)

Characteristic	Northstar (N=137)	Placebo (N=139)	Overall (N=276)
Gender (n [%])			
Male	45 (32.8)	51 (36.7)	96 (34.8)
Female	92 (67.2)	88 (63.3)	180 (65.2)
Age (Years) (n [%])			
< 65	118 (86.1)	119 (85.6)	237 (85.9)
≥ 65	19 (13.9)	20 (14.4)	39 (14.1)
Mean (SD)	47.6 (13.29)	47.3 (15.34)	47.4 (14.34)
Median	46.0	45.0	46.0
Range	19 - 80	18 - 85	18 - 85
Race (n [%])			
Caucasian	101 (73.7)	105 (75.5)	206 (74.6)
Black	30 (21.9)	28 (20.1)	58 (21.0)
Hispanic	1 (0.7)	2 (1.4)	3 (1.1)
Oriental	1 (0.7)	1 (0.7)	2 (0.7)
American Indian	0	1 (0.7)	1 (0.4)
Other	4 (2.9)	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)
Weight (kg)			
Mean (SD)	79.29 (17.992)	82.63 (22.360)	80.98 (20.342)
Median	78.90	77.10	77.10
Range	45.4 - 136.1	49.9 - 163.3	45.4 - 163.3
Height (cm)			
Mean (SD)	168.65 (10.049)	169.88 (10.365)	169.27 (10.210)
Median	167.60	167.60	167.60
Range	149.9 - 193.0	149.9 - 198.1	149.9 - 198.1

IV = intravenous; SD = standard deviation.

The two treatment groups were also similar with respect to medical history, concomitant conditions, previous and current medications. The following table from the final study report summarizes the concomitant medical conditions for the study population. The dermatological conditions were primarily “dry skin” and keratoses. None of the skin conditions would have been expected to affect the testing of the drug product provided the protocol was followed regarding patch application only on normal appearing skin. Table 5 from Protocol BDTS-99-67, pages 72 – 75 of the Final Study Report, summarizes the concomitant medications used by

subjects in each arm of the study. As indicated in Tables 9.1 – 9.4 (pages 84 - 87 of the final study report), there was no significant differences in the mean, median, standard deviation, or ranges for systolic and diastolic blood pressure, heart rate, and respiratory rate between either arm of the study – both at baseline and 10 minutes after the procedure. Laboratory work was not obtained as part of this study.

Table 13. Concomitant Medical Conditions (Table 4 from BDTS-99-67 Final Study Report, p. 58)

Body System	Placebo (N = 138) n (%)	Active (N = 136) n (%)
Ophthalmic	19 (13.8%)	10 (7.4%)
Otorhinolaryngologic	32 (23.2%)	34 (25.0%)
Drug Allergies	14 (10.1%)	21 (15.4%)
Endocrinologic	48 (34.8%)	48 (35.3%)
Dermatologic	27 (19.6%)	16 (11.8%)
Pulmonary	12 (8.7%)	18 (13.2%)
Cardiovascular	49 (35.5%)	55 (40.4%)
Gastrointestinal	47 (34.1%)	58 (42.6%)
Musculoskeletal	40 (29.0%)	37 (27.2%)
Neurologic	32 (23.2%)	5 (18.4%)
Genitourinary	72 (52.2%)	66 (48.5%)
Hematologic	13 (9.4%)	13 (9.6%)
Immunologic	5 (3.6%)	4 (2.9%)
Psychiatric	24 (17.4%)	25 (18.4%)
Total	133 (96.4%)	129 (94.9%)

6.3.1.12 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

6.3.1.13 Unplanned Analyses

No unplanned analyses were substituted for or added to the planned analyses.

6.3.1.14 Sponsor's Efficacy Results

6.3.1.14.1 Primary Efficacy Variables

The primary efficacy measure was the level of pain experienced immediately after venipuncture or IV cannulation. A 10-cm VAS was used to assess the level of pain. Mean VAS scores for both arms of the study are listed in the table below.

Table 14. Mean VAS scores post-procedure (Table 7 from BDTS-99-67 Final Study Report, p. 37)

VAS	Number (%) of Subjects	
	Northstar (N = 134)	Placebo (N = 136)
0 - 1	111 (82.8)	44 (32.4)
>1 - 2	8 (6.0)	33 (24.3)
>2 - 3	4 (3.0)	15 (11.0)
>3 - 4	2 (1.5)	10 (7.4)
>4 - 5	5 (3.7)	11 (8.1)
>5 - 6	2 (1.5)	7 (5.1)
>6 - 7	0	11 (8.1)
>7 - 8	2 (1.5)	3 (2.2)
>8 - 9	0	0
>9 - 10	0	2 (1.5)
Mean ¹ (SD)	0.77 (1.486)	2.53 (2.295)
Median	0.20	1.65
Range	0.0 - 7.8	0.0 - 10.0

¹P value was <0.001 based on the ANOVA model:

VAS score = Center + Procedure + Treatment + Error.

VAS = Visual Analogue Scale (0 - 10 cm); smaller scores indicate less pain.

SD = standard deviation.

The mean VAS score was significantly lower in the Northstar group than in the placebo group (mean VAS score $\pm$ SD: 0.77 ± 1.486 and 2.53 ± 2.295 , respectively; $P < 0.001$) indicating that on average, subjects treated with the Northstar system reported feeling significantly less pain than did subjects treated with the placebo system. Overall, more subjects in the Northstar group reported little or no pain (VAS scores 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 group experienced more severe pain; VAS scores of greater than 3 were observed in only 11 subjects treated with the Northstar system compared with 44 subjects treated with the placebo system.

6.3.1.14.2 Secondary Efficacy Variables

No secondary efficacy variables were evaluated in this study.

6.3.1.15 Discussion of Efficacy Findings in Study BDTS 99-67

Taken as a whole, the efficacy findings in Study BDTS 99-67 support the effectiveness of the Northstar system in providing local dermal analgesia on intact skin in the setting of venipuncture or intravenous cannulation in adults as measured by VAS scores. This finding is based on a statistically significant difference in the VAS scores between the placebo and Northstar groups, and on the number of patients who felt little or no pain. The clinical significance of the latter result, comparison of patients who felt little or no pain, may be more refined with a comparison of the numbers/percentages of patients who scored their pain in different groupings of VAS scores. The tables below were generated with the sponsor's data and compare the treatment responses at both ends of the pain spectrum, i.e., those who felt little pain and those who experienced a significant amount of pain.

Table 15. Pain Assessment by Therapy - Minimal Pain Levels (based on CRT data)

Treatment	VAS = 0cm (%) n (%)	VAS ≤ 1cm (%) n (%)	VAS ≤ 2cm (%) n (%)	VAS ≤ 3cm (%) n (%)
Placebo	6 (4)	44 (32)	77 (57)	92 (68)
Northstar	34 (25)	111 (83)	119 (89)	123 (92)

Table 16. Pain Assessment by Therapy – Maximal Pain Levels (based on CRT data)

Treatment	VAS ≥ 5cm (%) n (%)	VAS ≥ 6cm (%) n (%)	VAS ≥ 7cm (%) n (%)
Placebo	23 (17)	16 (12)	5 (4)
Northstar	5 (4)	5 (4)	2 (1)

These tables indicate that the Northstar treatment both decreased the percentages of patients experiencing significant amounts of pain and increased the percentages of those who experienced minimal to no pain compared to placebo.

Subset analyses by gender, race and age were performed by the Sponsor on the per protocol population. The tables below were derived from the data sets presented by the Sponsor and correspond with the Sponsor's calculations. In each subgroup, the mean VAS score was lower in those subjects who were given the Northstar system than those who received placebo, and there were no marked differences in groups.

Table 17. Subgroup Analysis (based on Sponsor's data)

Statistic	Female (n=178)		Male (n=92)	
	Northstar (n=92)	Placebo (n=86)	Northstar (n=42)	Placebo (n=50)
mean VAS	0.772	2.872	0.762	1.926
st. dev. VAS	1.610	2.477	1.188	1.815
Statistic	Caucasian		Black	
	Northstar (n=98)	Placebo (n=102)	Northstar (n=30)	Placebo (n=28)
mean VAS	0.701	2.391	1.050	2.875
st. dev. VAS	1.380	2.294	1.897	2.288
Statistic	<65 years of age (n= 234)		≥65 years of age (n= 36)	
	Northstar (n=117)	Placebo (n= 117)	Northstar (n= 17)	Placebo (n= 19)
mean VAS	0.745	2.622	0.933	1.918
st. dev. VAS	1.415	2.326	1.952	2.047

6.3.2 BDTs-99-68 A Double-blind Evaluation of the Northstar Lidocaine Iontophoretic Drug Delivery System in Pediatric Subjects

6.3.2.1 Overall Design and Summary of Findings

This study was a multicenter, randomized, placebo-controlled, double-blind, parallel group trial assessing the pain associated with patch removal and either venipuncture or insertion of an intravenous cannula (IV) in pediatric subjects. The placebo consisted of Northstar system in which the lidocaine hydrochloride was replaced with normal saline solution. Epinephrine was contained in both the Northstar system and the placebo. Pain was assessed immediately after the patch was removed and immediately after procedure using a Nine-Face Interval Scale (NFIS) scored by the subject. In addition, pain was assessed using the NFIS by a parent or guardian of each child age 5 through 11 years old and by the patients, ages 12 to 17 years old, using Visual Analog Scale (VAS).

A total of 272 subjects were randomized and 249 subjects completed the study. There was no significant difference in NFIS scores by investigator compared to those of the parent/guardian, and VAS scores between placebo and Northstar system immediately following patch removal. The subjects who were treated with the Northstar system had significantly less pain, ($p<0.001$) by investigator recorded NFIS scores, than the recipients of the placebo immediately following the procedure. Similarly, Northstar treated patients experienced less pain immediately following their procedures compared to recipients of placebo, as measured by parent/guardian recorded NFIS scores and self-reported VAS scores in the older children. When analyzed according to gender, race or age, the results were similar in all subpopulations, which included male and female, white and Hispanic, and age groups including 5-7 year olds, 8-11 year olds and 12-17 year olds.

6.3.2.2 Study Plan

The original version of this protocol was dated October 10, 2000. Three amendments were made, amendment 1 was dated November 28, 2000, amendment 2 which was dated February 28, 2001 and amendment 3 which was dated March 30, 2001. The first subject was entered on January 4, 2001 and the last subject completed the study on June 21, 2001.

Source: NDA submission, Clinical Study Report for Protocol No.: BDTS-99-68 pp. 1, 38

6.3.2.3 Objectives

The protocol-specified objective of the study was:

“to demonstrate the safety and efficacy of the Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar) compared with a placebo system when used for local dermal — on intact skin in children aged 5 to 17 years. A secondary objective was to assess pain experienced during removal of the patch, due to the adhesive.”

6.3.2.4 Design

In this clinical study, the Northstar system was to be tested for its ability to decrease the pain felt by subjects undergoing a routine venipuncture for phlebotomy or intravenous (IV) cannulation. The study was to compare the Northstar system, administering 10% lidocaine and 0.1% epinephrine, with an otherwise identical placebo system in which lidocaine was replaced with sodium chloride (NaCl). The anode of the placebo patch was to contain 1.05 mg epinephrine per patch, as was the active patch.

The protocol was to be designed as a randomized, double-blind, parallel-group, placebo-controlled, prospective, multicenter clinical study. Each subject was to receive a single treatment with either a Northstar or a placebo system approximately 15 minutes before a scheduled venipuncture or intravenous (IV) cannulation procedure. Skin at the application site was to be examined for dermal reactions immediately following removal of the patch system. Subjects were to evaluate 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 subjects 5 to 11 years of age were to record 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 was to assess their pain using a Visual Analogue Scale (VAS). Pain experienced during removal of the patch, due to the adhesive, was to be assessed by all subjects and parent(s)/guardians in the same manner using the same scales. Each subject was to return to the center 24 ± 8 hours later so that the treatment area could be assessed again for dermal reactions.

6.3.2.5 Primary Efficacy Variable

The primary efficacy variable was to be the level of pain experienced from the venipuncture/IV cannulation procedure as reported by the subjects using the Nine-Face Interval Scale (NFIS).

6.3.2.6 Secondary Efficacy Variables

Subjects ages 12 to 17 years were to assess their procedural pain using a 10-cm Visual Analog Scale (VAS). Pain scores with VAS ranged from 0 to 10 with 0 representing “no pain” and 10 representing “severe Pain.” In addition, the parent or guardian of each subject aged 5 to 11 years old was to use the NFIS to assess their child’s pain.

Lastly, the level of pain associated with the removal of the test device was to be assessed. The same scales used to evaluate the pain from the procedure were to be used again in this part of the protocol.

6.3.2.7 Population

Patients were to be selected from both in-patients and out-patients presenting for routine venipuncture or intravenous cannulation. Patients were to be grouped into three classes by age: 5-7, 8-11, and 12-17 years of age. Classes were to be approximately equal in size at each investigative site. The following criteria were to be used in patient selection.

Inclusion Criteria:

- male or female between 5 and 17 years of age, inclusive
- in the opinion of the Investigator, was medically stable
- were willing to complete all study procedures
- parent(s)/guardian(s) were capable of understanding and signing a written informed consent form, and if able to read and comprehend, the patient was to sign a written assent form
- available for the study days
- the expected duration for IV cannulation was 12 hours or less

Exclusion Criteria:

- obvious skin imperfections (moles, marks, bruises, cuts, abrasions, discolorations, or abnormalities) on the test site
- excessive hair, which in the opinion of the Investigator, would interfere with patch adhesion (clipping or shaving of hair is not permitted)
- known sensitivity to amide anesthetics and/or epinephrine
- pregnant or lactating females
- has had a needle stick 24 hours prior to baseline visit (Visit 1)
- current or history of dermal conditions that contraindicate use of iontophoretic treatment, such as skin allergy or hypersensitivity to metals and/or adhesives, electrodes and other components of the patch, active dermatitis, petechial hemorrhagic areas, and/or easy bruising
- current or history of systemic conditions that contraindicated use of iontophoretic treatment, such as any systemic vasculitis

- current or history of a medical condition that would contraindicate treatment with the product, such as neurological disorders, psychological disorders, psychiatric disorders, or other conditions which, in the opinion of the Investigator, placed the patient at risk or had the potential to confound interpretation of the study results
- presence of implanted or externally mounted electrical or electronic medical devices (i.e., pacemakers, transcutaneous electrical nerve stimulation [TENS] units, etc.)
- history of fainting, arrhythmia or irregular pulse
- treatment with iontophoresis or participation in venipuncture/IV cannulation, investigational product, or patch testing studies within 30 days prior to this study
- use of any medication having an analgesic effect (such as aspirin and other non-steroidal anti-inflammatory drugs) not allowed 24 hours prior to study treatment and until all pain assessments were complete. Regular strength, over-the-counter Tylenol could be taken at the labeled doses up to 12 hours before treatment.
- use of systemic or topical corticosteroids, not including nasal or inhaled corticosteroids, within 3 weeks before treatment.

Participants could be withdrawn from the study at their own request for any reason, at the request of a parent or guardian, or at the discretion of the principal investigator, or for any of the following reasons:

- There was an indication that the patient had an allergic reaction to Northstar (e.g. hives, itching, anaphylaxis, low blood pressure, bronchospasm, or edema)
- There was an indication of toxicity from the test article (e.g. numbness of the tongue, lightheadedness, visual disturbance, muscular twitching, or convulsion)
- Incomplete delivery of Northstar treatment, either active or placebo, as indicated by the incomplete delivery light being illuminated on controller during the iontophoretic delivery cycle or if manual discontinuation occurs for any other reason. In instances of incomplete delivery, patches were to be examined to determine the effectiveness of the adhesion.
- Patient was non-compliant or uncooperative
- Patient was lost to follow-up
- Patient was discovered to be a protocol violator
- It was determined by the investigator to be in the patient's best interest
- Administrative reasons, including but not limited to:
 - Failure to return for follow-up visits.
 - Termination of the trial by the sponsor.

6.3.2.8 Methods and Procedures

The table below (taken from Table 2 from the Protocol BDTS-99-68 Final Study Report), provides the details of the data to be collected according to the study phase. Following initial evaluation, randomization, and instruction on assessing pain using the NFIS, and if applicable, the VAS, the patch was to be applied to the test site (Visit 1). The site was to be cleaned with alcohol and allowed to dry. Test sites were not to be shaved or clipped of excess hair, and were to be marked with an indelible marker to facilitate locating the anode and cathode sites at follow-up (Visit 2). The patch was to be attached to the controller, which delivered a 10-minute treatment. After treatment, before removal, the patch was to be examined for effectiveness of the

adhesion. The patch was then to be removed. The patient, and parent/guardian if applicable, then were to record pain assessment (Nine-Face Interval Scale and VAS). All patients were to record their experience independently or with the assistance of study personnel only. Similarly, parent/guardian responses were not to be shown to the patient. Between 5 and 10 minutes after patch removal, but before venipuncture or IV cannulation, the treatment site was to be evaluated for erythema and edema using the Draize scale. Venipuncture with a 22-gauge needle or a 23-gauge winged blood collection set, or IV cannulation with a 22-gauge needle was then to be performed and pain assessments were to be repeated immediately afterward. Vital signs were to be obtained and instructions were to be given regarding problems to look for and what to do if one should arise. The site was to be evaluated again at 24 hours after the start of treatment.

Table 18. Study Schedule (Table 2 from BDTS-99-68 Final Study Report, p.133)

Procedures	Visit 1 (Day 1)			Visit 2 (Day 2)
	Baseline	Post-patch	Post-Venipuncture/ IV Cannulation	
Obtain Informed Consent/Assent	X			
Verify Inclusion/Exclusion	X			
Demography	X			
Vital signs (heart rate, oral or tympanic temperature, respirations, blood pressure, height, weight)	X		X ^a	
Medical history	X			
Urine pregnancy test	X ^b			
Examine test site	X			
Venipuncture/IV Cannulation		X		
Nine-Face Interval Scale (Pain assessment by patient – all ages)		X	X	
Nine-Face Interval Scale (Observer Assessment by parent, ages 5-11 year olds)		X	X	
VAS (Pain assessment by patients aged 12-17 years)		X	X	
Draize Scale (Visual Scoring of Dermal Reaction)		X		X
Concomitant Medication Assessment	X ^c			X
Adverse Event Assessment		X	X	X

^aPost-venipuncture/IV cannulation vital signs include blood pressure, heart rate, and respirations.

^bFor females of childbearing potential.

^cConcomitant medication assessment should include all medications used 30 days before Visit 1.

Adverse events of erythema and edema at the site of patch application were to be collected in the CRF using the Draize Score (scores from 0 to 4) criteria. Erythema and edema were to be reported as AEs only when the Draize Score was recorded as 4. Patients who had a Draize score of 4 at any timepoint were to be further evaluated by the investigator to assess whether they had received a 'burn' from exposure to the test article. As part of the assessment of burns, all patches were to be examined before removal to determine the effectiveness of the adhesion. Adhesion was to be scored according to the following table (taken from Table 4 of the Protocol BDTS-99-68 Final Study Report).

Table 19. Adhesion Scoring (Table 4 from BDTS-99-68 Final Study Report, p. 137)

Description	Score
90-100% adhered (essentially no lift off of the skin)	0
75% - < 90% adhered (some edges only lifting off of the skin)	1
50% - 75% adhered (less than half of the system lifting off the skin)	2
< 50% adhered but not detached (more than half of the system lifting off the skin without falling off)	3
Patch detached (patch completely off the skin)	4

All events which were determined to be a burn related to the test article were to be investigated by the Sponsor to determine the mode of injury: electrical contact, pH change, loss of (anode) contact, or other. As part of the investigation, the test articles associated with identified burns were to be returned to the Sponsor for evaluation.

6.3.2.9 Analysis Plan

The efficacy analysis was to be based on the Intent-to-Treat (ITT) population, defined as all subjects who received the study treatment and evaluated their pain after a procedure. Data for all randomized subjects who received treatment with either the Northstar or the placebo systems were to be included in the safety analyses. Summaries of subject disposition, demographic and baseline characteristics, concomitant medications, NFIS scores (primary efficacy), VAS scores, Draize scores, AEs, and vital signs were to be tabulated by treatment.

6.3.2.9.1 Analysis of Efficacy

The subjects in all age groups were to assess pain using the NFIS at two time points: immediately after removal of the patch, and immediately after venipuncture/IV cannulation (analgesia). In the 2 younger age groups (5 to 7 and 8 to 11 years), a parent(s)/guardian(s) also was to complete the same scale to record their perception of the pain the subject experienced. As a supplemental measure, subjects in the 12- to 17-year-old age group also were to assess their pain during the post-treatment interval by using a 10-cm VAS. All subjects (and parent(s)/guardian(s) where applicable) were to be taught how to use the scales to assess pain before any testing began, and were to be reminded of the technique before each evaluation. The

primary assessment of efficacy (analgesia) was to be the NFIS assessment completed by the subject immediately after venipuncture/IV cannulation. In addition to the raw NFIS (A – I), a weighted NFIS (McGrath, PA, et al) were to be calculated as A=0.08, B=0.22, C=0.34, D=0.47, E=0.60, F=0.78, G=0.82, H=0.90 and I=0.97.

An ordinal logistic regression was to be used to compare the difference between the two treatments with regard to the NFIS score recorded both immediately following patch removal and post-venipuncture/IV cannulation. The analysis for the post-venipuncture/IV cannulation was to be performed as the primary efficacy assessment. The model to be used was:

NFIS = Center (C) + Procedure (P) + Treatment (T) + Age (A) + residual

(The 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.)

6.3.2.9.2 Determination of Sample Size

The Sponsor offered the following basis for determination of sample size. The determination was based on detecting a difference of 0.9 VAS score units between groups. VAS scores however, neither were the primary efficacy endpoint, nor used by all groups studied. No justification for taking this approach was proffered.

The original version of the protocol called for

“A sample size of 125 patients per group will yield at least 90% power to detect a difference of 1 score unit between groups, assuming a common standard deviation of 2.0 units.”

This was modified in the first amended protocol to state that

“Approximately 275 subjects were to be enrolled at approximately 6 investigative sites to obtain at least 250 evaluable subjects (125 subjects in each treatment group). This number would yield at least 90% power to detect a difference of 0.9 VAS score units between groups, using a 2-sided test at the 5% significance level, assuming a common standard deviation of 2.2 units.”

Approximately equal numbers of subjects were to be enrolled at each site, with no more than 60 subjects at any site. Subjects were to be grouped into three categories by age: 5 to 7, 8 to 11, and 12 to 17 years of age. Roughly equal numbers of subjects were to be enrolled in each group, and no group was to comprise more than 40% of the total enrollment at any single center. Roughly equal numbers of each procedure were to be performed at each site for each age group, and neither procedure was to comprise >40% of the enrollment for that investigative site.

In order to achieve study enrollment, centers that were able to enroll additional subjects were allowed to do so during the course of the trial. Enrollment at one center (#0014) exceeded the limit of 60 subjects, while the remaining sites enrolled less than 60 subjects. This was noted as a protocol deviation, but was approved by _____ because it would not affect the final statistical analysis.

A completed subject was one who had both Visit 1 and Visit 2 evaluations. Subjects who did not return for Visit 2 evaluations were to be replaced after consultation with the Sponsor or the Sponsor's representative.

6.3.2.10 Protocol Amendments and Changes in the Planned Analysis

There were three amendments to the study protocol dated 28 November 2000, 28 February 2001, and 30 March 2001. The following changes were made at those times:

Changes Effective 28 November 2000:

- The Sponsor's name was updated to Drug Delivery Technologies, Inc., from Becton Dickinson Transdermal Systems.
- To ensure appropriate randomization within each procedure, the randomization was split by procedure and age.
- More detailed information was added to the Draft Product Labeling section.
- The exclusion criteria were modified as follows:
 - excluded subjects who participated in IV cannulation studies within the 30 days prior to the study
 - disallowed the use of medications with analgesic effect the 48 hours prior to study treatment and until all pain assessments were complete, and
 - allowed nasal or inhaled corticosteroids.
- A clarification was added that temperature could be measured orally or tympanically.
- A concomitant medication assessment was added at Baseline and Visit 2.
- Clarification was added to the discussion of Draize scoring regarding follow-up for dermal effects.
- Clarification was added to identify that burns that were related to the test article would be investigated by the Sponsor.
- Needle sizes were changed to allow for 22-gauge needles or 23-gauge winged blood collection sets (butterfly) to be used in the procedure.
- The statistical analyses were amended to include an ordinal logistic regression of Draize scores to be performed to evaluate dermal effect. The linear model to be used was as follows: Center+Procedure+Treatment+Age+C*T+P*T+A*T+residual.
- The Cochran-Mantel-Haenszel mean score test was to be performed as a secondary analysis.
- The sample size assumptions were revised to detect a difference in the 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.
- Blood pressure and respiration rate were added to the vital sign assessments described in the ICF.

Changes Effective 28 February 2001:

- The Sponsor's name was updated to Vyteris, Inc., from Drug Delivery Technologies (formerly Becton Dickinson Transdermal Systems).
- A statement was added that all subjects who completed the first visit would be included in the efficacy evaluable population and analyzed.
- The visit window for Visit 2 was extended to 24±8 hours.

Changes Effective 30 March 2001:

- The use of any medication having an analgesic effect (such as aspirin or other NSAIDs) was reduced from 48 to 24 hours before study treatment and until all pain assessments were complete.
- Regular-strength, over-the-counter Tylenol ® (acetaminophen) was allowed to be taken at the labeled doses up to 12 hours before treatment, which was a change from 24 hours.

In addition to the above amendments, the Sponsor reported a single change in the planned analysis. Specifically, the ordinal logistic regression of Draize score was not performed because of the sparseness of the data.

None of these amendments was likely to have a significant effect on the final results of the trial or on the conclusions drawn from them.

6.3.2.11 Study Conduct

The study was conducted as planned with the exception of the protocol violations noted below. The Sponsor notes that the study was undertaken only after full approval of the clinical study protocol was obtained from an Institutional Review Board. The study was conducted in accordance with both Good Clinical Practice (GCP) Guidelines and the ethical principles included in the "Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; the 35th WMA General Assembly, Venice, Italy, October 1983; the 41st WMA General Assembly, Hong Kong, September 1989; the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. The Sponsor contracted with an independent organization, _____, to monitor this study and provide data quality assurance. To this end, recorded data, where available, were monitored to verify accuracy compared with the CRFs. Upon closeout of the study, a full audit was performed.

A database was prepared from data entered on the CRFs. Data security was ensured through password protection and regular backups of the data. Upon completion of the study and verification of the data, an audit of at least 10% of the database was conducted. Upon completion of the audit, the database was locked to prevent any additional changes. A copy of the locked database was provided to the _____ for statistical analysis.

6.3.2.11.1 Patient Disposition

Seven investigators enrolled 272 subjects (136 Northstar; 136 placebo) to receive treatment with the Northstar system (Northstar). A total of 249 (91.5%) subjects completed the study. Seven (2.6%) subjects discontinued treatment due to technical failure and 10 (3.7%) discontinued the study due to AEs. Three (1.1%) subjects were "lost to follow-up" and two (0.7%) subjects withdrew their consent to participate in the study. Of the 249 subjects who completed the study, 126 subjects were in the Northstar group, and 123 subjects were in the placebo group. The table below, taken from the final study report, shows subject disposition.

Table 20. Subject Disposition (Table 5 from BDTS-99-68 Final Study Report, p.41)

Subject Status	Northstar n (%)	Placebo n (%)	Total n (%)
Randomized	136 (100.0)	136 (100.0)	272 (100.0)
Safety Population (Received treatment)	136 (100.0)	135 (99.3)	271 (99.6)
Intent-to-Treat (ITT) Population	130 (95.6)	126 (92.6)	256 (94.1)
Completed	126 (92.6)	123 (90.4)	249 (91.5)
Prematurely Discontinued Study	10 (7.4)	13 (9.6)	23 (8.5)
Technical Failure	5 (3.7)	2 (1.5)	7 (2.6)
Adverse Event	4 (2.9)	6 (4.4)	10 (3.7)
Consent Withdrawn/Refused Further Treatment	0	2 (1.5)	2 (0.7)
Death	0	0	0
Protocol Violation	0	1 (0.7)	1 (0.4)
Lost to Follow-Up	1 (0.7)	2 (1.5)	3 (1.1)
Other	0	0	0

The following table lists the protocol violations, based on the inclusion and exclusion criteria, for this study. It was noted that the violations occurred in subjects who were randomized and completed the study.

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Table 21. Protocol Violations (Table 6 from BDTS-99-68 Final Study Report, p. 42)

Subject	Treatment	Violation
0007/1022	Placebo	Subject use of corticosteroid medications within the 3 weeks prior to the study
0007/2115A	Active	Subject use of medication having an analgesic effect (such as aspirin and other non-steroidal anti-inflammatory drugs) within 24 hours before and during the course of the study.
0008/1109	Placebo	Not available for the study days
0008/1209	Placebo	Not available for the study days
0009/1103	Placebo	Patient had needle stick within 1 hour of visit 1
0009/1239	Active	Subject use of corticosteroid medications within the 3 weeks prior to the study
0015/2045	Active	Expected duration for IV cannulation >12 hours
0015/2245 ^A	Placebo	Subject use of medication having an analgesic effect (such as aspirin and other non-steroidal anti-inflammatory drugs) within 24 hours before and during the course of the study.
0015/2246 ^A	Active	Subject use of medication having an analgesic effect (such as aspirin and other non-steroidal anti-inflammatory drugs) within 24 hours before and during the course of the study.

^AExclusion criterion # 12 was amended on 12 March 2001 disallowing the use of medication having an analgesic effect from within 48 hours prior to and during the course of the study to within 24 hours prior to the course of the study. Subject 0007/2115 was enrolled before the amendment; Subject 0015/2245 was enrolled after the amendment but still met the exclusion criterion and took analgesic medication within 24hrs prior to treatment; and Subject 0015/2246 was enrolled after the amendment but still met the exclusion criterion and took analgesic medication within 24hrs prior to treatment. No per-protocol analysis was performed by the sponsor, however with the overall size of the ITT population, it is not unreasonable to expect that these violations would not have significantly affected the results of the study.

In addition to the above, three subjects were randomized to the wrong age group and four subjects, including one who was randomized to the wrong age group, underwent the alternative procedure and not the one planned at enrollment. Two of the subjects were in the Northstar group; the remaining four were in the placebo group. All of these subjects completed the study; their actual ages and procedures performed were used for analysis of safety and efficacy.

Neither the reasons for prematurely discontinuing the study nor the protocol violations were expected to have a significant impact on the efficacy results. The numbers were evenly distributed between the Northstar and placebo groups, and the incidents cited were not suggestive of a systematic skewing of the population in either arm of the study.

6.3.2.12 Demographics/Group Comparability

The table below presents a summary of the demographic and baseline characteristics of all randomized subjects. Baseline height and weight measurement statistics were reported in Table 3.2 of the BDTS-99-68 Final Study Report, p. 75. Slightly more than half the subjects in each of the two treatment groups were males and Caucasians. The average age for all of the subjects was 10.3 years, and the range was 5 to 17 years. The distribution of subjects between Northstar and Placebo arms was similar in terms of subjects' gender, age, race, height, weight, and procedure.

Table 22. Demographics and Characteristics (Table 7 from BDTS-99-68 Final Study Report, p. 43)

Characteristic	Northstar (N=136)	Placebo (N=136)	Overall (N=272)
Gender (n [%])			
Male	73 (53.7)	73 (53.7)	146 (53.7)
Female	63 (46.3)	63 (46.3)	126 (46.3)
Age (Years) (n [%])			
5 - 7	38 (27.9)	34 (25.0)	72 (26.5)
8 - 11	48 (35.3)	50 (36.8)	98 (36.0)
12 - 17	50 (36.8)	52 (38.2)	102 (37.5)
Mean	10.2	10.4	10.3
SD	3.56	3.42	3.48
Median	10.0	10.0	10.0
Range	5 - 17	5 - 17	5 - 17
Race (n [%])			
Caucasian	77 (56.6)	77 (56.6)	154 (56.6)
Black	13 (9.6)	16 (11.8)	29 (10.7)
Hispanic	43 (31.6)	40 (29.4)	83 (30.5)
Oriental	1 (0.7)	1 (0.7)	2 (0.7)
Other	2 (1.5)	2 (1.5)	4 (1.5)
Procedure Planned			
Venipuncture	75 (55.1)	77 (56.6)	152 (55.9)
IV Cannulation	61 (44.9)	59 (43.4)	120 (44.1)

IV = intravenous; SD = standard deviation

The two treatment groups were also similar with respect to medical history, concomitant conditions, previous and current medications. The table below was taken from the final study report and summarizes the concomitant medical conditions for the study population. Table 5 from Protocol BDTS-99-68, pages 86 – 88 of the Final Study Report, summarizes by class the concomitant medications used by subjects in each arm of the study and indicates that the two treatment arms were similar. As indicated in Tables 9.1 – 9.4 (pages 105 - 108 of the final study report), there were no significant differences in the mean, median, standard deviation, or ranges for systolic and diastolic blood pressure, heart rate, and respiratory rate between either arm of the study and between baseline and 10 minutes following the procedure. Laboratory work was not obtained as part of this study.

Table 23. Concomitant Medical Conditions (Table 4 from BDTS-99-68 Final Study Report, p. 76)

Body System	Placebo (N = 135) n (%)	Active (N = 136) n (%)
Ophthalmic	5 (3.7%)	8 (5.9%)
Otorhinolaryngologic	30 (22.2%)	36 (26.5%)
Drug Allergies	7 (5.2%)	8 (5.9%)
Endocrinologic	12 (8.9%)	12 (8.8%)
Dermatologic	10 (7.4%)	14 (10.3%)
Pulmonary	25 (18.5%)	16 (11.8%)
Cardiovascular	5 (3.7%)	6 (4.4%)
Gastrointestinal	24 (17.8%)	22 (16.2%)
Musculoskeletal	15 (11.1%)	17 (12.5%)
Neurologic	31 (23.0%)	21 (15.4%)
Genitourinary	14 (10.4%)	10 (7.4%)
Hematologic	3 (2.2%)	5 (3.7%)
Immunologic	12 (8.9%)	15 (11.0%)
Psychiatric	15 (11.1%)	8 (5.9%)
Total	104 (77.0%)	94 (69.1%)

6.3.2.13 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

6.3.2.14 Unplanned Analyses

There were no unplanned analyses substituted for the planned efficacy analyses.

6.3.2.15 Sponsor's Efficacy Results

6.3.2.15.1 Primary Efficacy Variables

The primary efficacy variable for this study was pain associated with venipuncture or intravenous cannulation. The NFIS score completed by the investigator immediately after the procedure served as the primary assessment of efficacy.

A weighted NFIS score was also calculated using A=0.08, B=0.22, C=0.34, D=0.47, E=0.60, F=0.78, G=0.82, H=0.90, and I=0.97, where “A” indicated a laughing happy subject and “I” indicated a crying upset subject.

The distribution of NFIS scores assessed by the investigators immediately following patch removal and immediately after the procedure are presented in the table below for all the subjects combined.

Table 24. NFIS Pain Assessments (all age groups) (Table 8 from BDTS-99-68 Final Study Report, p. 45)

Nine-Face Interval Scale	Number (%) of Subjects			
	Immediately Post-Patch Removal		Immediately Post-Procedure	
	Northstar (N = 130)	Placebo (N = 126)	Northstar (N = 130)	Placebo (N = 126)
A (1)	51 (39.2)	47 (37.3)	37 (28.5)	15 (11.9)
B (2)	15 (11.5)	22 (17.5)	25 (19.2)	18 (14.3)
C (3)	18 (13.8)	20 (15.9)	19 (14.6)	16 (12.7)
D (4)	21 (16.2)	8 (6.3)	17 (13.1)	13 (10.3)
E (5)	13 (10.0)	14 (11.1)	15 (11.5)	27 (21.4)
F (6)	5 (3.8)	7 (5.6)	8 (6.2)	16 (12.7)
G (7)	3 (2.3)	6 (4.8)	4 (3.1)	10 (7.9)
H (8)	2 (1.5)	1 (0.8)	1 (0.8)	4 (3.2)
I (9)	2 (1.5)	1 (0.8)	4 (3.1)	7 (5.6)
p-value¹	0.938		<0.001	

¹p-value was based on the ordinal logistic regression with the model: score = site, procedure, age group, and treatment.

Subjects treated with the Northstar system experienced significantly less pain from the venipuncture/IV cannulation procedures than did subjects treated with the placebo system ($p<0.001$). There were no significant treatment-group differences in the distribution of NFIS scores immediately following patch removal ($p=0.938$). In the following table, pain assessment by age groups is presented.

Table 25. NFIS Pain Assessments by Age Groups (Table 6.1 from BDTS-99-68 Final Study Report, p. 89)

NINE FACE INTERVAL SCALE	Placebo (N = 126)			Active (N = 130)		
	5-7 years (N=28)	8-11 years (N=49)	12-17 years (N=49)	5-7 years (N=35)	8-11 years (N=45)	12-17 years (N=50)
Immediately Post Patch Removal						
A(1)	12 (42.9%)	19 (38.8%)	16 (32.7%)	17 (48.6%)	19 (42.2%)	15 (30.0%)
B(2)	2 (7.1%)	10 (20.4%)	10 (20.4%)	3 (8.6%)	4 (8.9%)	8 (16.0%)
C(3)	4 (14.3%)	7 (14.3%)	9 (18.4%)	8 (22.9%)	5 (11.1%)	5 (10.0%)
D(4)	0	1 (2.0%)	7 (14.3%)	3 (8.6%)	6 (13.3%)	12 (24.0%)
E(5)	2 (7.1%)	8 (16.3%)	4 (8.2%)	2 (5.7%)	6 (13.3%)	5 (10.0%)
F(6)	4 (14.3%)	2 (4.1%)	1 (2.0%)	1 (2.9%)	1 (2.2%)	3 (6.0%)
G(7)	4 (14.3%)	1 (2.0%)	1 (2.0%)	0	2 (4.4%)	1 (2.0%)
H(8)	0	0	1 (2.0%)	0	2 (4.4%)	0
I(9)	0	1 (2.0%)	0	1 (2.9%)	0	1 (2.0%)
Immediately Post Procedure						
A(1)	5 (17.9%)	5 (10.2%)	5 (10.2%)	10 (28.6%)	15 (33.3%)	12 (24.0%)
B(2)	0	10 (20.4%)	8 (16.3%)	6 (17.1%)	9 (20.0%)	10 (20.0%)
C(3)	2 (7.1%)	8 (16.3%)	6 (12.2%)	4 (11.4%)	4 (8.9%)	11 (22.0%)
D(4)	3 (10.7%)	4 (8.2%)	6 (12.2%)	4 (11.4%)	5 (11.1%)	8 (16.0%)
E(5)	5 (17.9%)	9 (18.4%)	13 (26.5%)	3 (8.6%)	6 (13.3%)	6 (12.0%)
F(6)	4 (14.3%)	6 (12.2%)	6 (12.2%)	3 (8.6%)	2 (4.4%)	3 (6.0%)
G(7)	3 (10.7%)	3 (6.1%)	4 (8.2%)	2 (5.7%)	2 (4.4%)	0
H(8)	0	3 (6.1%)	1 (2.0%)	1 (2.9%)	0	0
I(9)	6 (21.4%)	1 (2.0%)	0	2 (5.7%)	2 (4.4%)	0

There was no apparent difference between the placebo-treated and Northstar-treated groups in the discomfort observed when the patches were removed. At the time of the procedures, there was on average, significantly less pain, as determined by NFIS, for patients in each age group who were treated with the Northstar system.

6.3.2.15.2 Secondary Efficacy Variables

Secondary measures were also evaluated. The NFIS scores assessed by a parent(s)/guardian(s) were used for the 2 younger age groups (5 to 7 and 8 to 11 years) and the 10-cm VAS scores were used by older subjects (12 to 17 years of age) to measure the pain of patch removal and the level of pain associated with the procedure.

As indicated in the table below, the assessment of pain by the parent(s)/guardian(s) immediately following the procedure was consistent with the NFIS scores assessed by the investigators. Statistically significantly less pain was experienced with the Northstar system compared with the placebo system ($p=0.001$) based on ordinal logistic regression. As previously observed, there were no significant treatment group differences in the distribution of NFIS scores immediately following patch removal ($p=0.595$).

Table 26. Pain Assessment by Parent/Guardian Based on NFIS by Age Groups (Table 6.3 from BDTs-99-68 Final Study Report, p. 91)

Nine Face Interval Scale	Placebo (N = 77)		Active (N = 80)	
	5-7 years (N=28)	8-11 years (N=49)	5-7 years (N=35)	8-11 years (N=45)
Immediately Post Patch Removal				
A(1)	9 (32.1%)	7 (14.3%)	5 (14.3%)	9 (20.0%)
B(2)	3 (10.7%)	15 (30.6%)	8 (22.9%)	13 (28.9%)
C(3)	2 (7.1%)	6 (12.2%)	9 (25.7%)	5 (11.1%)
D(4)	4 (14.3%)	6 (12.2%)	5 (14.3%)	5 (11.1%)
E(5)	3 (10.7%)	10 (20.4%)	6 (17.1%)	8 (17.8%)
F(6)	6 (21.4%)	5 (10.2%)	1 (2.9%)	3 (6.7%)
G(7)	0	0	1 (2.9%)	0
H(8)	1 (3.6%)	0	0	2 (4.4%)
Immediately Post Procedure				
A(1)	2 (7.1%)	4 (8.2%)	4 (11.4%)	7 (15.6%)
B(2)	0	6 (12.2%)	6 (17.1%)	8 (17.8%)
C(3)	3 (10.7%)	8 (16.3%)	10 (28.6%)	14 (31.1%)
D(4)	4 (14.3%)	10 (20.4%)	1 (2.9%)	2 (4.4%)
E(5)	7 (25.0%)	6 (12.2%)	3 (8.6%)	3 (6.7%)
F(6)	5 (17.9%)	6 (12.2%)	4 (11.4%)	3 (6.7%)
G(7)	2 (7.1%)	6 (12.2%)	2 (5.7%)	3 (6.7%)
H(8)	2 (7.1%)	3 (6.1%)	4 (11.4%)	3 (6.7%)
I(9)	3 (10.7%)	0	1 (2.9%)	2 (4.4%)

In the group of patients 12 to 17 years of age, the VAS pain scores collected reflected the same findings as noted above. There was no significant difference in the pain experienced by those who received the placebo versus those who received the Northstar system immediately following patch removal ($p=0.184$). There was significantly less pain experience in the Northstar group (meanVAS=2.584) than in the placebo group (meanVAS=1.502) following the procedure ($p=0.015$). Additionally, more patients treated with the Northstar system (29 subjects [58%])

reported feeling little or no pain with the procedure (VAS score of 1 or less) compared to subjects treated with the placebo system (16 subjects [32.7%]).

6.3.2.16 Discussion of Efficacy Findings in Study BDTS 99-68

The efficacy findings in Study BDTS 99-68 support the effectiveness of the Northstar system in providing local dermal analgesia on intact skin in pediatric subjects ages 5 through 17 years undergoing venipuncture or intravenous cannulation. With the use of the Northstar system, the NFIS scores associated with the procedure were similar to those associated with the removal of the patch for both arms of the study.

Subset analyses by gender, race and age were performed by the Sponsor. The tables below subgroup the data by race and gender and compare the Northstar system to placebo for pain felt on removal of the patch and immediately after the procedure.

Table 27. Subgroup Analysis by Race (Table 68.1 from ISE, p. 82)

Nine Face Interval Scale	Placebo (N = 126)			Active (N = 130)		
	Caucasian (N=73)	Hispanic (N=35)	Other* (N=18)	Caucasian (N=76)	Hispanic (N=39)	Other* (N=15)
Immediately Post Patch Removal						
A(1)	24 (32.9%)	17 (48.6%)	6 (33.3%)	26 (34.2%)	17 (43.6%)	8 (53.3%)
B(2)	9 (12.3%)	9 (25.7%)	4 (22.2%)	11 (14.5%)	3 (7.7%)	1 (6.7%)
C(3)	13 (17.8%)	4 (11.4%)	3 (16.7%)	8 (10.5%)	8 (20.5%)	2 (13.3%)
D(4)	6 (8.2%)	1 (2.9%)	1 (5.6%)	15 (19.7%)	5 (12.8%)	1 (6.7%)
E(5)	10 (13.7%)	2 (5.7%)	2 (11.1%)	9 (11.8%)	2 (5.1%)	2 (13.3%)
F(6)	4 (5.5%)	2 (5.7%)	1 (5.6%)	2 (2.6%)	3 (7.7%)	0
G(7)	5 (6.8%)	0	1 (5.6%)	2 (2.6%)	0	1 (6.7%)
H(8)	1 (1.4%)	0	0	2 (2.6%)	0	0
I(9)	1 (1.4%)	0	0	1 (1.3%)	1 (2.6%)	0
Immediately Post Procedure						
A(1)	5 (6.8%)	9 (25.7%)	1 (5.6%)	20 (26.3%)	13 (33.3%)	4 (26.7%)
B(2)	8 (11.0%)	6 (17.1%)	4 (22.2%)	13 (17.1%)	8 (20.5%)	4 (26.7%)
C(3)	9 (12.3%)	5 (14.3%)	2 (11.1%)	11 (14.5%)	7 (17.9%)	1 (6.7%)
D(4)	7 (9.6%)	2 (5.7%)	4 (22.2%)	11 (14.5%)	5 (12.8%)	1 (6.7%)
E(5)	20 (27.4%)	5 (14.3%)	2 (11.1%)	12 (15.8%)	2 (5.1%)	1 (6.7%)
F(6)	13 (17.8%)	2 (5.7%)	1 (5.6%)	3 (3.9%)	3 (7.7%)	2 (13.3%)
G(7)	4 (5.5%)	3 (8.6%)	3 (16.7%)	3 (3.9%)	0	1 (6.7%)
H(8)	2 (2.7%)	2 (5.7%)	0	0	1 (2.6%)	0
I(9)	5 (6.8%)	1 (2.9%)	1 (5.6%)	3 (3.9%)	0	1 (6.7%)

* The majority of subjects were black.

Table 28. Subgroup Analysis by Gender (Table 68.4 from ISE, p. 85)

Nine Face Interval Scale	Placebo (N = 126)		Active (N = 130)	
	Male (N=67)	Female (N=59)	Male (N=69)	Female (N=61)
Immediately Post Patch Removal				
A(1)	29 (43.3%)	18 (30.5%)	25 (36.2%)	26 (42.6%)
B(2)	7 (10.4%)	15 (25.4%)	13 (18.8%)	2 (3.3%)
C(3)	9 (13.4%)	11 (18.6%)	14 (20.3%)	4 (6.6%)
D(4)	3 (4.5%)	5 (8.5%)	6 (8.7%)	15 (24.6%)
E(5)	8 (11.9%)	6 (10.2%)	7 (10.1%)	6 (9.8%)
F(6)	5 (7.5%)	2 (3.4%)	1 (1.4%)	4 (6.6%)
G(7)	5 (7.5%)	1 (1.7%)	1 (1.4%)	2 (3.3%)
H(8)	0	1 (1.7%)	1 (1.4%)	1 (1.6%)
I(9)	1 (1.5%)	0	1 (1.4%)	1 (1.6%)
Immediately Post Procedure				
A(1)	11 (16.4%)	4 (6.8%)	19 (27.5%)	18 (29.5%)
B(2)	9 (13.4%)	9 (15.3%)	15 (21.7%)	10 (16.4%)
C(3)	7 (10.4%)	9 (15.3%)	10 (14.5%)	9 (14.8%)
D(4)	8 (11.9%)	5 (8.5%)	6 (8.7%)	11 (18.0%)
E(5)	14 (20.9%)	13 (22.0%)	10 (14.5%)	5 (8.2%)
F(6)	9 (13.4%)	7 (11.9%)	4 (5.8%)	4 (6.6%)
G(7)	4 (6.0%)	6 (10.2%)	1 (1.4%)	3 (4.9%)
H(8)	1 (1.5%)	3 (5.1%)	0	1 (1.6%)
I(9)	4 (6.0%)	3 (5.1%)	4 (5.8%)	0

From a clinical perspective, comparisons between the placebo and active arms of numbers of patients experiencing little or no pain and those experiencing severe pain may be more meaningful. The table below compares these two ends of the pain spectrum for the ITT population grouped by age, race and gender. NFSI values of “A” through “C” were used to indicate little or no pain, and values of “G” through “I” were used to indicate severe pain. Comparisons were made for pain experienced with patch removal and with the procedure. The percentage of patients falling within each NFSI grouping is listed.

Table 29. Comparison of Minimal and Maximal Pain By Subgroups (based on Sponsor's data)

Subgroup	NFSI subgroups Immediately Post Patch Removal				NFSI subgroups Immediately Post Procedure			
	% (A – C)		% (G – I)		% (A – C)		% (G – I)	
	Placebo	North-star	Placebo	North-star	Placebo	North-star	Placebo	North-star
Age range:								
5-7 y	64	80	14	3	25	57	32	14
8-11 y	73	62	4	9	47	62	14	9
12-17 y	71	56	4	4	39	66	10	0
Race								
Caucasian	63	59	10	7	30	58	15	8
Hispanic	86	72	0	3	57	72	17	3
Other	72	73	6	7	39	60	22	13
Gender								
Male	67	75	9	4	40	64	13	7
Female	75	52	3	7	37	61	20	7

The table demonstrates no apparent differences between the placebo and Northstar arms of the study in terms of pain felt immediately following patch removal. In contrast for each subcategory of age, race and gender, a greater percentage of patients felt little or no pain with the Northstar system versus placebo, and a lesser percentage of patients felt severe pain with the Northstar system versus placebo, immediately following the procedure.

6.3.3 Other Controlled Clinical Studies

In addition to the two pivotal trials reviewed above, six controlled clinical studies were conducted using the to-be-marketed version of the Northstar system, Market Image Patch (MIP) III. Some of these studies were designed to evaluate efficacy for indications other than intravenous cannulation and venipuncture, _____, and to fulfill the requirements of the combination rule. Five trials were conducted in adults only, one evaluated pediatric and adult subjects, and one studied pediatric patients only. All the studies were prospective, randomized, double-blinded and placebo-controlled. Each is described below.

6.3.3.1 BDTS-99-24 Dermal Depth of Anesthesia Produced by the Northstar Iontophoretic Lidocaine Drug Delivery System

This was a single center, prospective, placebo-controlled, double-blinded Phase I clinical trial. Twenty Caucasian adults were evaluated, each receiving two treatments in a single visit. Only Caucasian subjects were included due to technical limitations of the optically-based erythema-measuring device utilized. 76% of the subjects were women. The two treatments included an

active Northstar System treatment (lidocaine 100mg with 1.05mg of epinephrine) and a placebo treatment (an active patch containing epinephrine only); one administered to each forearm in a sequential fashion.

6.3.3.1.1 Objectives

The primary objective of this study was to quantify the depth to which clinically meaningful anesthesia penetrated the skin immediately after treatment with Northstar, as compared to placebo.

Secondary objectives were twofold; to measure the depth to which perception of pressure is eliminated after treatment with Northstar compared to placebo, and to measure the degree of anesthetic effect over time after active and placebo treatment, from both pain and sensory perspectives.

6.3.3.1.2 Methods

Once the first treatment site was identified, skin temperature and thickness were assessed. Baseline erythema and cutaneous pain (CP) assessments were completed. A baseline Sensory Threshold Depth (SD) and Pain Threshold Depth (PD) were measured. The first Northstar System (active or placebo) was applied and activated according to the draft instructions for use. At completion of the treatment cycle, the patch was removed and SD and PD were assessed. CP, erythema and skin temperature were subsequently measured. All measurements were repeated at 15, 30 and 60 minutes after removal of the patch. Skin reactions were graded by Draize evaluation at the 60-minute timepoint. All procedures were repeated on the contralateral forearm with the other (active or placebo) treatment. Subjects were seen approximately 24 hours later for repeat Draize evaluation of the skin.

6.3.3.1.3 Results

The pain depth threshold immediately after patch removal was significantly greater for the active device versus placebo, 6.37mm versus 3.01mm, $p < 0.0001$ (one sided). With increasing time following treatment, the difference in PD threshold increased between the two arms as shown in the table below.

Table 30. Pain Depth Data (Table 11.4 from BDTS-99-24 Integrated Clinical & Statistical Report p. 27)

	Baseline		T=15		T=30		T=60	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
N	20	20	20	20	20	20	20	20
Mean (mm)	2.91	3.16	9.38	2.87	10.33	3.24	10.68	3.35
Max (mm)	5.08	6.49	25.00	4.74	25.00	6.16	24.30	11.86
Min (mm)	1.01	1.52	3.30	1.19	4.93	0.98	4.22	0.72
SD	1.13	1.22	6.31	1.07	5.18	1.36	6.35	2.35
Difference†	-0.26		6.51		7.09		7.33	
95% limit‡			4.03		4.61		4.85	

†- Difference of the means (Active - Placebo), in millimeters.

‡ - lower bound of the 95% confidence limit for the difference, in millimeters.

The results for Sensory Threshold Depth immediately following treatment and 15, 30 and 60 minutes later yielded time course results similar to the PD results above. There was a significantly greater mean sensory threshold depth to any sensation in the active treatment group at all times following treatment compare to the placebo group.

The levels of pain and sensory depth with active treatment peaked at about 15 minutes following the treatment and persisted for at least one hour. There were no adverse events reported for this study.

6.3.3.1.4 Discussion of Efficacy Findings

The results of BDTS-99-24 support the efficacy of the Northstar System for

6.3.3.2 BDTS-99-25 In-House Evaluation of a Developmental Iontophoretic Placebo Patch for Study of the Northstar Iontophoretic Lidocaine Patch

This was a single-center, prospective, single-blind Phase I clinical trial. The study was designed to compare analgesia and dermal effects of three test systems, one fully active and two placebo systems, when used in healthy adult subjects undergoing venipuncture or intravenous cannulation. This study was used to determine the more appropriate placebo for later use in double-blinded studies. The study was conducted from April 20, 1999 to April 22, 1999.

6.3.3.2.1 Objectives

The primary objective of this study was to compare the degree of blanching produced by the active Northstar treatment to that produced by the Active Placebo. Secondary objectives were twofold: compare the degree of analgesia produced by the Active Placebo and the Passive Placebo, and to compare the dermal effects of the Active Northstar treatment and the Active Placebo.

6.3.3.2.2 Methods

Thirty-six adult subjects (63% women, 87% Caucasian) received four treatments; one to the dorsum of each hand and one to each antecubital fossa. Treatments consisted of an Active Northstar Treatment, where the controller is active and the patch contains lidocaine 100mg with 1.05mg of epinephrine, Active Placebo, where the controller is active and the patch contains 1.05mg of epinephrine but no lidocaine, and Passive Placebo, where the controller is inactive and the patch contains lidocaine 100mg with 1.05mg of epinephrine. All subjects received all three test articles (and one duplicate for the fourth site), delivered in random order and location. All treatments were completed at a single visit. Blanching, analgesia and dermal effects were assessed at each treatment site. Subjects were to be seen approximately 24 hours later for repeat Draize evaluation of the skin.

The first treatment site was identified from the randomization schedule, and the masked test article was applied and activated. After completion of treatment, the degree of skin blanching was graded at the target site and skin reactions were assessed by Draize evaluation. Venipuncture or cannulation was performed according to standard phlebotomy practice, although no therapy was instilled and no blood was withdrawn. The volunteer documented the pain he or she experienced from the procedure on a 10-cm Visual Analog Scale (VAS). The process was then repeated at sites 2, 3 and 4. Draize evaluation of all sites was performed again before the volunteers were discharged for the day. Subjects were seen approximately 24 hours later for repeat Draize evaluation of the skin. If effects were observed at this visit, the volunteer was to be re-assessed at 48 hours post-treatment, then as required by clinical need.

6.3.3.2.3 Results

There was a significant difference in blanching between the active devices and the passive placebo. Only the passive device resulted in any occurrence of no blanching and resulted in 100% no blanching on the hand. The extent of blanching between the active devices was not significantly different ($p=0.529$) at the two sites of application. There was no statistically significant difference in the overall mean VAS scores between the passive placebo and the active placebo (2.97 versus 3.89, $p=0.109$). The overall mean VAS score for the active Northstar system was 1.26, which was significantly different from the two placebo treatments. The table below indicates that the active Northstar system on average provided better pain control than either the active or the passive placebo at both sites.

Table 31. VAS Score Data (Table 1.13 from BDTS-99-25 Integrated Clinical & Statistical Report p. 45)

Site	VAS Scores (cm on a 10 cm scale)											
	active Northstar (n=42)				active Placebo (n=44)				passive Placebo (n=42)			
	Avg	Max	Min	s.d.	Avg	Max	Min	s.d.	Avg	Max	Min	s.d.
Overall	1.11	10.00	0.00	1.97	3.82	9.50	0.12	2.72	2.97	9.36	0.00	2.77
Elbow	0.61	3.65	0.00	1.03	2.48	7.10	0.12	2.09	1.54	7.88	0.00	1.93
Hand	1.53	10.00	0.00	2.44	5.16	9.50	0.60	2.65	4.69	9.36	0.54	2.67

Although no severe adverse events were reported in this study, one patient suffered a mild burn that required 7 days for recovery without treatment. Additionally, no VAS score was reported for seven applications of the Northstar System, two of the active placebos and three of the passive placebos. The reasons given for the Northstar System included burn at patch site after removal – no venipuncture performed, incomplete delivery, subject felt “queasy” and faint, and no comments.

The table below indicates the pain response to the procedures based on treatment. As with the other studies, two categories are evaluated: little to no pain as indicated by VAS scores of ≤ 3 and severe pain as indicated by VAS scores of ≥ 7 . The Northstar System was associated with significantly more subjects having little or no pain and significantly fewer subjects having severe pain than either of the two placebo therapies.

Table 32. Summary VAS Score Data (based on Sponsor’s data)

Site	VAS Score Groupings [n (%)]					
	active Northstar (n=43)		active Placebo (n=49)		passive Placebo (n=48)	
	VAS ≤ 3 cm	VAS ≥ 7 cm	VAS ≤ 3 cm	VAS ≥ 7 cm	VAS ≤ 3 cm	VAS ≥ 7 cm
all	39 (91)	0 (0)	27 (55)	7 (9)	21 (44)	6 (13)

6.3.3.2.4 Discussion of Efficacy Results

This study was designed to evaluate the appropriateness of the active placebo in terms of providing blanching similar to the active Northstar system while producing a level of analgesia similar to placebo. The study succeeded in terms of the blanching effect, but it could be argued that a more appropriate comparison for analgesia would have been a patch with neither lidocaine nor epinephrine and a controller that produced no current. The only cause for concern using the proposed placebo in future studies is possible hypersensitization of skin by iontophoretic application of epinephrine. This study was not designed to detect such a possibility. The study did however clearly indicate that lidocaine and electrical current improve the analgesia provided by the device.

6.3.3.3 BDTs-00-16 Efficacy of the Northstar Iontophoretic Lidocaine Drug Delivery System for Anesthesia Prior to Treatment of Dermal Lesions by Laser

This was a randomized, double-blind, parallel-group, placebo-controlled, prospective, multicenter, Phase III clinical study evaluating the safety and efficacy of the Northstar system in providing analgesia for patients undergoing laser ablation of superficial skin lesions.

6.3.3.3.1 Objectives

The objective of this study was to demonstrate the safety and efficacy of the Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar) compared to placebo when used for local dermal analgesia on intact skin, prior to the treatment of superficial lesions by laser.

6.3.3.3.2 Methods

The study was conducted between March 13 and May 11, 2001. There were 66 subjects in the intent-to-treat population; 76% were female, 90% were Caucasian, and 15% were between 5 and 18 years old.

All subjects were naïve to laser treatment before study enrollment. Each subject was to receive a single treatment with either a Northstar or a placebo system. The laser procedure was to be performed within 20 minutes from the completion of drug delivery (i.e., 10 to 30 minutes from the start of the controller.) Intradermal injection of lidocaine during the surgical procedure was permitted at the request of the subject, or, if in the opinion of the investigator, supplemental analgesia was needed.

All subjects evaluated the pain they experienced from the procedure using a 10-cm Visual Analog Scale (VAS). They also completed an Ordered Category Anesthesia Scale (OCAS, see table below) designed specifically for this study to describe the sufficiency of analgesia. The clinician performing the procedure also completed a VAS of their perception of the subject's pain during the procedure. In addition, the physician was to assess the percentage of the original treatment plan that was completed at the time that any additional anesthesia was required.

VAS scores were weighted using the Investigator's estimate of the percentage of the procedure that was completed at the time of additional analgesia as a factor. It was calculated as:

$$\text{weighted VAS} = [\text{VAS} * (1 + (1 - \text{percent of procedure completed}))]$$

Thus the primary efficacy variable, the weighted VAS score, would be equal to the unweighted VAS score if the subject completed the procedure without supplemental analgesia. The weighted VAS would be double the unweighted VAS if the subject required supplemental analgesia before the procedure could begin.

A supplemental analysis, a non-parametric ANCOVA, was performed on ranked VAS pain scores, including center, treatment and center-by-treatment interaction as factors and subject age as a covariate. This supplemental analysis was not originally planned in the protocol.

Skin at the application site was examined for dermal reactions following removal of the patch system. Each subject returned to the center approximately 24 (± 4) hours after treatment to assess the condition of the skin in the treatment area. Additional visits were required if dermal effects (Draize score =3), considered to be clinically significant by the Investigator, persisted at the first follow-up visit. If this occurred, the subject was to be followed until the effects were resolved, or, in the opinion of the Investigator, the event was no longer considered clinically significant.

Table 33. Ordered Category Anesthesia Scale (Table 2 from BDTS-00-16 Clinical Study Report p. 27)

Description	Score
Intolerable Pain: Severe pain	6
Moderate Pain: Interferes with most activities	5
Mild Pain: Might interfere with daily activities to a small degree	4
Mild Discomfort: Would not interfere with daily activities	3
Noticeable Sensation: Mild to no discomfort	2
Possibly Some Sensation: Possible sense of pressure or touch only	1
No Sensation: Unable to feel contact to region	0

6.3.3.3.3 Results

The table below summarizes the VAS score data reported by the subjects immediately after the procedure. The overall mean ($\pm$ SD) VAS score was lower in subjects in the Northstar treatment group compared with subjects in the placebo treatment group (1.57 ± 2.57 versus 3.72 ± 2.49 , respectively).

Within both treatment groups, children reported higher mean VAS scores than did the adults. In the placebo group, children had a mean score of 4.87 and adults had a mean score of 3.60. Similarly, in the Northstar treatment group, children had a mean score of 3.13 and adults had a mean score of 1.16.

Results were similar for the weighted VAS scores. The mean ($\pm$ SD) weighted VAS score was lower in subjects in the Northstar treatment group compared with subjects in the placebo treatment group (2.04 ± 4.30 versus 4.55 ± 3.64 , respectively). Based on the ANCOVA model, the difference between the two treatment groups for mean weighted pain VAS score was not statistically significant ($p=0.380$). The supplemental analysis based on the ranked VAS pain scores was also performed. The results from this analysis showed the VAS pain scores in the Northstar group were statistically significantly lower than the placebo group ($p=0.004$). This was because 2 of 7 subjects treated with the Northstar system in the smaller center (0011) had VAS pain scores that were higher than the other subjects in that treatment group (9.9 and 10.0 for

these two subjects versus 0.0-0.3 for the rest of subjects). Ranked VAS pain scores reduced the deviations of the mean score within the treatment groups.

Table 34. Subject VAS Score Results (from Table 8 of BDTS-00-16 Clinical Study Report p. 43)

Pain Assessment Score	Placebo (N=32) n (%)			Northstar (N=34) n (%)			p-value ³
	Children ¹ (n=3)	Adults ² (n=29)	All (n=32)	Children (n=7)	Adults (n=27)	All (n=34)	
VAS (cm)							
Mean	4.87	3.60	3.72	3.13	1.16	1.57	
SD	3.332	2.436	2.494	3.872	2.020	2.567	
Median	5.40	3.60	3.70	1.40	0.40	0.40	
Range	1.3 - 7.9	0.0 - 8.7	0.0 - 8.7	0.0 - 10.0	0.0 - 9.9	0.0 - 10.0	
Weighted VAS ⁴							
Mean (± SD)	7.000	4.294	4.548	4.286	1.460	2.042	0.380
SD	6.6461	3.2893	3.6420	6.5512	3.4427	4.2996	
Median	5.400	4.600	4.600	1.400	0.400	0.400	
Range	1.30 – 14.3	0.00 – 14.3	0.00 – 14.3	0.00 – 18.1	0.00 – 17.9	0.00 – 18.1	

Note: For subjects who had supplemental analgesia during the procedure, the Visual Analogue Scale (VAS) was evaluated prior to the administration of supplemental analgesia; the VAS is based on a 10-cm scale where 0 = no pain and 10 = severe pain.

¹Children = aged <18 years

²Adults = aged ≥18 years

³The p-value is based on the analysis of covariance (ANCOVA) model: weighted VAS = center, age, treatment, and center-by-treatment.

⁴Weighted VAS = VAS*(1+ [1 -% of procedure completed])

The results for the physician assessment of pain based on the VAS scale and the OCAS scores reported by the subjects are similar to those for subject reported VAS scores. The tables below summarize these results.

Table 35. Physician VAS Score Results (Table 10 from BDTS-00-16 Clinical Study Report p.46)

Pain Assessment Score	Placebo (N=32)			Northstar (N=34)			p-value
	Children ¹ (n=3)	Adults ² (n=29)	All (n=32)	Children (n=7)	Adults (n=27)	All (n=34)	
VAS (cm)							
Mean	7.03	4.51	4.75	3.50	1.47	1.89	
SD	0.404	2.871	2.831	4.212	2.529	2.993	
Median	7.10	5.10	5.35	0.60	0.30	0.35	
Range	6.6 – 7.4	0.0 – 8.6	0.0 – 8.6	0.0 – 10.0	0.0 – 9.9	0.0 – 10.0	
Weighted VAS ³							
Mean	8.950	5.554	5.873	4.657	1.771	2.365	0.255
SD	3.4011	4.4262	4.4105	6.6830	3.7387	4.5317	
Median	7.400	5.100	5.350	0.600	0.300	0.350	
Range	6.60 – 12.8	0.00 – 15.5	0.00 – 15.5	0.00 – 18.1	0.00 – 17.9	0.00 – 18.1	

Note: For subjects who had supplemental analgesia during the procedure, the Visual Analogue Scale was evaluated before the administration of supplemental analgesia.

¹Children = aged <18 years

²Adults = aged ≥18 years

³weighted VAS = VAS*(1+ [1 -% of procedure completed])

The p-value is based on the ANCOVA model: Weighted VAS = center, treatment, age, center-by-treatment.

Table 36. OCAS Score Results (Table 11 from BDTS-00-16 Clinical Study Report p. 47)

Ordered Category Anesthesia Scale Score	Placebo (N=32) n (%)		Northstar (N=34) n (%)		p-value ³
	Children ¹ (n=3)	Adults ² (n=29)	Children (n=7)	Adults (n=27)	
Intolerable Pain (6)	0	1 (3.1)	1 (2.9)	1 (2.9)	<0.001
Moderate Pain (5)	0	6 (18.8)	0	0	
Mild Pain (4)	2 (6.3)	6 (18.8)	1 (2.9)	0	
Mild Discomfort (3)	1 (3.1)	10 (31.3)	1 (2.9)	4 (11.8)	
Noticeable Sensation (2)	0	1 (3.1)	2 (5.9)	9 (26.5)	
Possible Some Sensation (1)	0	4 (12.5)	0	7 (20.6)	
No Sensation (0)	0	1 (3.1)	2 (5.9)	6 (17.6)	

¹Children = aged <18 years

²Adults = aged ≥18 years

³p-value based on Cochran-Mantel-Haenszel test controlling for site and age group.

The results from the supplemental analysis showed the VAS pain score in the Northstar group were statistically significantly lower than the placebo group ($p=0.004$). This was because two of seven subjects treated with the Northstar system in the smaller center had VAS pain scores that were higher than the other subjects in that treatment group (9.9 and 10.0 for these two subjects versus 0.0-0.3 for the rest of subjects). Ranked VAS pain scores reduced the deviations of the mean score within the treatment groups resulting in a significant difference between groups.

6.3.3.3.4 Discussion of Efficacy Results

For all of the variables measured, subject-assessed VAS score, physician-assessed VAS score, and OCAS scores, there was less pain experienced by patients who received the Northstar system than who received the placebo. The table below compares the raw VAS scores for the children and adults separately in the same manner as for the pivotal trials. There are more Northstar patients in both groups who experienced minimal-to-no pain compared to placebo, and fewer who experienced moderate-to-severe pain compared to placebo.

Table 37. Comparison of Patient Assessed Pain Levels by Age Groups (based on Sponsor's data)

Patient's Age	VAS Scores n(%)			
	Placebo (n=29)		Northstar (n=27)	
	≤ 3	≥ 7	≤ 3	≥ 7
<18 years	1 (33)	1 (33)	4 (57)	1 (14)
≥ 18 years	13 (45)	3 (10)	23 (85)	1 (4)

Analysis of the data indicated that 9/66 (14%) subjects required supplemental anesthesia in order to complete their procedure. Of these, seven (11%) were 20% of the way through the procedure and two (3%) were 40% of the way through the procedure before requiring the supplemental treatment.

Although these data appear to support efficacy for providing analgesia for laser treatment of superficial dermatological lesions, the study called for comparison of the Northstar treatment with placebo using analysis of covariance on VAS pain scores. Based on this planned analysis of the primary efficacy variable, the study failed to demonstrate a significant difference between the two treatments ($p=0.380$).

6.3.3.4 98NS 01-09 Blinded Prospective Evaluation of a Lidocaine Iontophoretic Delivery System

This was a double-blind, randomized, placebo- and active-controlled, parallel-group, crossover, single center study evaluating the analgesia produced by iontophoresis of lidocaine and epinephrine on the hands and antecubital fossa. Comparison was made between the Market

Image Patch III (MIP III, proposed for marketing), the MIP II, and a placebo system – MIP II and MIP III without current.

6.3.3.4.1 Objectives

The primary objective of this study was to compare the degree of analgesia produced by iontophoresis of lidocaine and epinephrine on the hands using the MIP III as opposed to the previously tested MIP II, and to compare both to placebo (the same patches but with no applied current).

Additionally, the degree of analgesia produced by iontophoresis of lidocaine and epinephrine at the antecubital site using MIP III was compared to placebo.

The secondary objectives of this study were to compare sensation of iontophoresis (SAI), pain on patch removal (PRP), degree of analgesia produced by both placebo systems at both sites, range of motion, and dermal effects (including bruising).

6.3.3.4.2 Methods

The study was conducted on a total of 61 adult subjects of whom, 44 (55% male; 75% Caucasian) were evaluable. The study was conducted between July 29 and July 31, 1998.

Subjects were randomly assigned to receive four patch treatments, one to each hand and one to each antecubital. All of the antecubital treatments were with the MIP III patches (active treatment at one antecubital and placebo treatment at the other). Whereas, subjects received both MIP II and MIP III treatments on their hands according to the following treatment combination scheme:

Table 38. Treatment Combination Scheme (from page 12 of the Clinical Study Report)

Treatment Group	One Hand	Other Hand	One Antecubital	Other Antecubital
1	active MIP III	active MIP II	active MIP III	placebo ¹ MIP III
2	active MIP III	placebo ¹ MIP II	active MIP III	placebo ¹ MIP III
3	placebo ¹ MIP III	active MIP II	active MIP III	placebo ¹ MIP III

¹Placebo indicates no current.

Eligible subjects received all four of their assigned treatments at a single visit (the protocol did not specify a time sequence for administering the treatments) followed by either venipuncture (antecubital) or intravenous cannulation (hand) near or at the treatment site. Efficacy was assessed during iontophoresis, immediately following iontophoresis, and immediately following patch removal. Subjects evaluated venipuncture/cannulation pain using a 10-cm Visual Analog

Scale (VAS). The intensity and quality of the iontophoretic sensation, and pain upon patch removal were evaluated using a 21-point logarithmic scale where a score of 0 indicated no pain and a score of 18 indicated extreme pain. The quality of the iontophoretic sensation was assessed before patch removal using a Hedonic 21-point balanced VAS (range: -10 to +10) with 0 representing neutral sensation, pleasant sensations indicated by positive scores and unpleasant sensations indicated by negative scores. The range of motion in the hands was assessed by a range of motion writing exercise, and dermal effects at all of the treatment sites were evaluated by Draize scoring. Dermal effects were evaluated every 24 to 48 hours post-treatment for up to 4 days. Subjects with persistent symptoms were to be evaluated every 96 hours until their symptoms resolved.

6.3.3.4.3 Results

A total of 61 subjects were randomized and received some portion of the treatments. Sixteen subjects were prematurely withdrawn due to "high skin impedance" defined as receiving less than 95% of the desired current charge (17·mA·min). Data from these subjects were excluded from all analyses along with that of one subject who received the incorrect treatment schedule.

Analgesia at the antecubital site, with MIP III patches, was significantly greater ($p=0.0001$) following active treatment compared to placebo treatment. Similarly, significant differences were seen between active and placebo treatments on the hands, where active treatment was always superior regardless of comparator patch system. Comparison of analgesia by patch system indicated that active treatment with the MIP III patch was not significantly different from that provided by the MIP II patch. Likewise, the mean VAS scores for the placebo versions of each patch were similar.

Sensation intensity during iontophoresis at the antecubital site, with the MIP III patch, was significantly greater ($p=0.0001$) following active treatment compared to placebo treatment. Similarly, significant differences were seen between active and placebo treatments on the hands, where active treatment was generally associated with significantly ($p=0.0001$) greater intensity regardless of comparative placebo patch on the hands. Comparison of sensation intensity by patch, showed that the MIP III patch was associated with less sensation during iontophoresis than the MIP II patch although this difference was not statistically significant. Comparison of the quality of sensation by patch showed that active treatment with the MIP III patch was not significantly different from the MIP II patch.

Evaluation of pain on patch removal indicated no statistically significant difference between active and placebo treatment with the MIP III patch as well as between active treatment with the MIP II and MIP III patches.

The range of motion evaluations were listed, but the data were not analyzed nor were they amenable to meaningful analysis. The evaluations consisted of drawing Xs through circles and circles around Xs.

6.3.3.4.4 Discussion of Efficacy Results

There was a statistically significant difference in patient assessed pain scores between both Northstar System patches and their corresponding placebos. The table below evaluates the different patch systems by extremes of the pain scale, little or no pain versus severe pain, and by application site. For both versions of the Northstar System, MIP II and MIP III, the results were similar. More patients experienced little or no pain with their procedures at the sites with active treatments than at the sites of placebo treatments. Conversely, fewer patients experienced severe pain at the sites of active treatment than at the sites of placebo therapy. Both results support clinical efficacy of the Northstar Systems. It was noted that these data come from patients with skin impedance levels that were considered adequately low for inclusion. In addition, 13 VAS scores assessments were not recorded in the study; all were from the active treatment arms of the study, five were from the MIP II and eight were from MIP III. The reason(s) for the missing data was not provided.

Table 39. Comparison of Pain Levels by Patch Version & Application Site (from Sponsor's data)

Procedure Site	MIP II				MIP III			
	VAS ≤ 3		VAS ≥ 7		VAS ≤ 3		VAS ≥ 7	
	Placebo	North-star	Placebo	North-star	Placebo	North-star	Placebo	North-star
Hands	[n=19] 10 (53%)	[n=37] 24 (65%)	[n=19] 1 (5%)	[n=37] 1 (3%)	[n=18] 9 (50%)	[n=41] 28 (68%)	[n=18] 2 (11%)	[n=41] 0 (0%)
Arms	-	-	-	-	[n=54] 35 (65%)	[n=54] 48 (89%)	[n=54] 2 (4%)	[n=54] 0 (0%)
All	[n=19] 10 (53%)	[n=37] 24 (65%)	[n=19] 1 (5%)	[n=37] 1 (3%)	[n=72] 44 (61%)	[n=95] 76 (80%)	[n=72] 4 (6%)	[n=95] 0 (0%)

This study supports the claim of providing analgesia for venipuncture and intravenous cannulation. There were 16 subjects, 26% of those randomized, who were excluded from the analysis of efficacy due to "high skin impedance," i.e., the device was unable to deliver the

charge required for successful iontophoretic delivery of drug. Based on the data tables, nine failures occurred with the MIP III, six occurred with the MIP II and one was not clearly indicated but likely the MIP III as that was the last one administered. The Sponsor did not consider withdrawal from the study due to "high skin impedance" an adverse event and therefore did not submit CRFs or provide details of the instances where it occurred. For the study, 223 treatments were administered, including the 16 failed treatments, out of the planned 244. Thus, the "high skin impedance problem occurred in 7% of the treatments administered. Although no injuries were associated with the high impedance condition, and the device warns of its occurrence, further study of the situation by the Sponsor could possibly have led to a means of decreasing its incidence, e.g., better skin preparation or site selection.

6.3.3.5 98NS 01-10 A Double-Blind Comparative Evaluation of the Northstar Iontophoretic System to Placebo in Pediatric Subjects

This was a randomized, double-blind, placebo-controlled, single-center, pediatric study designed to compare the analgesia provided by the Northstar system with a placebo system when used in pediatric subjects before venipuncture. The study was conducted from January 27, 1999 through March 26, 1999.

6.3.3.5.1 Objectives

The primary objective of this study was to compare the efficacy of the Northstar Iontophoretic System (MIP-III patch) after a single application of lidocaine HCl and epinephrine to placebo (administration of the patch with no current), when applied to the antecubital area, in providing local analgesia prior to venipuncture in pediatric subjects. In addition, the safety of Northstar System in pediatric subjects was assessed.

6.3.3.5.2 Methods

Forty-nine pediatric subjects ages 5 to 17 years old (55% female and 82% Caucasian, 16% black) were stratified according to age group and randomized to Northstar System or placebo patch in a 1:1 ratio. Prior to a scheduled venipuncture procedure, each subject received a single treatment with either the Northstar System containing lidocaine HCl 100 mg and epinephrine 1.0 mg or a placebo treatment, the Northstar System with no current applied. Iontophoresis was performed for 10 minutes with a total current of 17 mA-min.

Skin at the application site was examined for dermal reactions immediately following removal of the patch. All subjects evaluated the pain they experienced from the venipuncture procedure using a Nine-Face Interval Scale (NFIS). Subjects 12 years of age and older also evaluated the pain that they experienced using a 10-cm Visual Analog Scale (VAS). Subjects were to complete the pain assessments before application of the patch, immediately following removal of the patch but before blood was drawn, and after blood was drawn (venipuncture). Each subject

returned to the center 16 to 48 hours later so that the treatment area could be assessed again for dermal reactions.

The CHEOPS Behavioral Assessment and Overall Experience Questionnaire were used by the investigator to measure the child's emotional responses after blood was drawn. The CHEOPS Behavioral Assessment is used to measure pain in children based on 6 types of behavior related to the experience of pain: crying, facial expression, verbal expression, torso position, touch, and leg position. The rating scale used in this study ranged from 6 (suggesting no painful responses) to 28 (suggesting an extreme response to pain, e.g., screaming and requiring restraint). Draize scores for erythema and edema were evaluated immediately after patch removal and 24 hours after the study treatment.

6.3.3.5.3 Results

Forty-nine subjects completed the study; 48 were evaluable for efficacy. One subject was enrolled in violation of an exclusion criterion. The subjects were stratified by age into three groups: 5 - 7 years old, 8 - 11 years old, and 12 - 17 years old.

With respect to the pain experienced during patch removal, there were no significant differences in the NFIS data between the subjects administered the Northstar System and subjects who received the placebo treatment ($p=0.280$). The results were comparable among all age groups. Overall, the mean level of pain experienced during cannulation was significantly less for subjects administered the Northstar System than for subjects in the placebo treatment group ($p=0.015$). This effect was observed among the three age groups. The table below summarizes the results of this study.

Table 40. Summary of NFIS Pain Assessments (Table 6 from the 98NS01-10 Clinical Study Report p.50)

All Age Groups:							
	Northstar		Placebo		Odds Ratio	p-value	95% CI²
Type of Pain	N¹	Mean	N	Mean			
Cannulation	23	2.83	25	4.32	0.27	0.015	(0.09, 0.78)
Patch Removal	23	3.04	25	3.60	0.57	0.280	(0.2, 1.58)
Age 5 to 7 Years:							
	Northstar		Placebo				
Type of Pain	N	Mean	N	Mean			
Cannulation	6	2.83	7	4.86			
Patch Removal	6	3.67	7	4.43			
Age 8 to 11 Years:							
	Northstar		Placebo				
Type of Pain	N	Mean	N	Mean			
Cannulation	9	2.50	8	3.88			

Patch Removal	9	3.11	8	3.38			
Age 12 to 18 Years:							
	Northstar		Placebo				
Type of Pain	N	Mean	N	Mean			
Cannulation ³	8	2.63	10	4.30			
Patch Removal ⁴	8	2.50	10	3.20			

¹Subject No. 92 was not evaluated for efficacy due to violation of exclusion criterion.

²CI = confidence interval.

³Pearson correlation coefficient for NFIS and VAS was 0.773 (p=0.000).

⁴Pearson correlation coefficient for NFIS and VAS was 0.727 (p=0.001).

Overall, mean total CHEOPS scores were low, and there were no notable differences between treatment groups or among age groups in the levels of distress displayed by the subjects. More subjects in the Northstar group than in the placebo group evaluated the blood collection experience with the patch system as better than previous venipuncture experiences. Similarly, parents/guardians evaluated their child's venipuncture experience as better with the patch system compared with previous experiences. Phlebotomists and nurses generally noted no difference for venipuncture experiences with the patch system as comparable to other blood drawing.

6.3.3.5.4 Discussion of Efficacy Results

The data reflect a statistically significant difference in the pain experienced with the two treatments for all age groups. Translating this to clinical significance is perhaps more difficult, but comparison of extreme responses to the procedures for each of the treatments provides insight into their efficacy. The table below compares the number of subjects in each treatment group that experienced minimal to no pain (NFIS scores A-C) and severe pain (NFIS scores G-I).

Table 41. Comparison of Pain Levels by Treatment (based on Sponsor's data)

Age Group	Minimal Pain (NFIS Scores A-C)		Severe Pain (NFIS Scores G-I)	
	Placebo (n=75)	Northstar System (n=72)	Placebo (n=75)	Northstar System (n=72)
all ages	42 (56%)	51 (71%)	6 (8%)	3 (4%)
5-7 years	13 (62%)	12 (67%)	5 (24%)	2 (11%)
8-11 years	12 (50%)	17 (63%)	1 (4%)	1 (4%)
12-18 years	17 (57%)	22 (81%)	0 (0%)	0 (0%)

For each age group and for all groups combined, a greater percentage of patients were seen to have little or no pain if given the Northstar System compared to the placebo treatment. In the youngest age group, a smaller percentage was seen to experience severe pain if they received the Northstar System compared to placebo treatment. In the older age groups, no difference was

noted in the percentages that experienced severe pain, but the percentages were very small most likely reflecting greater emotional maturity in these age groups.

The results of this study support the claim of efficacy for providing analgesia in pediatric subjects 5 years of age and older for the purpose of venipuncture.

6.3.3.6 98NS 01-11 Blinded Prospective Evaluation of a Lidocaine Iontophoretic Delivery System

This was a partially double-blind, randomized, placebo-controlled, parallel-group, single center study designed to compare the analgesia provided by the Northstar System (MIP III) to placebo for venipuncture or intravenous cannulation in adults. The study was considered “partially double-blind” because although neither the subject nor the nurse evaluating the dermal effects was informed of the treatment identity, blanching at the treatment site following electrical stimulation of the skin could reveal the type of treatment administered. The study was conducted from November 12, 1998 to November 13, 1998.

6.3.3.6.1 Objectives

The primary objective of this study was to compare the degree of analgesia produced by iontophoresis of lidocaine HCl and epinephrine using the Northstar System with placebo (Northstar System with no current) when applied to the dorsum of the hand and the antecubital space.

The secondary objectives of this study were to compare dermal effects (including bruising), the discomfort associated with patch removal (PRP), and the degree of analgesia produced by both treatments at all sites.

6.3.3.6.2 Methods

Forty-eight adults (60% female and 81% Caucasian, 10% Asian) were randomized to receive one of two treatment combinations as outlined in the table below. All four treatments were administered on a single visit and followed by intravenous cannulation to the hand sites and venipuncture to the antecubital sites.

Table 42. Treatment Combination Scheme (Table 1 from 98NS 01-11 Clinical Study Report p. 12)

Treatment Group	One Hand	Other Hand	One Antecubital	Other Antecubital
1	active MIP III	active MIP III	active MIP III	placebo ¹ MIP III
2	active MIP III	placebo ¹ MIP III	active MIP III	active MIP III

¹Placebo indicates no current.

Efficacy was evaluated immediately following patch removal, immediately following venipuncture/cannulation using a 10-cm linear visual analogue scale (VAS) score, at discharge (day of treatment), and 24 hours post-treatment. Subjects evaluated the level of PRP using a 21-point logarithmic scale where a score of 0 indicated no pain and higher scores indicated increased pain. The study nurse assessed dermal effects (including bruising) utilizing Draize scoring at all of the treatment sites at patch removal, at discharge, and at 24 hours post-treatment. Subjects with persistent symptoms were to be evaluated again at 48 hours post-treatment and every 96 hours until their symptoms resolved.

6.3.3.6.3 Results

The protocol was modified to use a generalized linear model approach to analyze the VAS score data as the assumption of normality was violated. In addition, the Gracely scale of 0 to 20 was used to assess the PRP instead of the 21-point scale.

The tables below show the mean VAS scores by site and treatment and the related statistical analysis results.

Table 43. VAS Score Data Summary (Table 5 from 98NS 01-11 Clinical Study Report p.25)

Antecubital				Hand Dorsum				Combined			
Active		Placebo		Active		Placebo		Active		Placebo	
N	Mean	N ¹	Mean	N	Mean	N	Mean	N	Mean	N	Mean
72	0.66	23	3.23	72	1.60	24	3.97	144	1.13	47	3.61

¹Data not included for one assessment completed two hours post-venipuncture.

Table 44. VAS Score Statistics Summary (Table 6 from 98NS 01-11 Clinical Study Report p.26)

Factor	Comparison	P-Value
Treatment	Active versus placebo (all sites combined)	0.0001
	Active versus placebo (antecubital)	0.0001
	Active versus placebo (hand dorsum)	0.0001
Site/Challenge Type	Antecubital (venipuncture) versus hand dorsum (cannulation)	0.0042
Side	Left side versus right side (all treatments combined)	0.9917
	<i>Interaction between treatment and site/challenge type</i>	0.0306

GENMOD with factors for treatment, subject, order of administration and hand/antecubital.

Anesthesia was significantly ($p = 0.0001$) greater following active treatment compared to placebo treatment regardless of treatment site or challenge type. An evaluation by treatment site

showed significantly greater pain ($p = 0.0042$) was experienced on the hand dorsum following cannulation challenge than at the antecubital following venipuncture challenge regardless of the treatment type. When the factors “treatment” and “site/challenge type” were considered together, a significant treatment-by-site interaction ($p = 0.0306$) was detected.

The results of the evaluation for pain on patch removal (PRP) indicated that overall, active treatment was associated with similar or greater PRP than placebo treatment. However, these differences were not statistically significant. Comparison of PRP by patch shows that active treatment with the MIP III patch was associated with less pain on patch removal than active treatment with the MIP II patch. However, this difference was not statistically significant.

6.3.3.6.4 Discussion of Efficacy Results

As with previous studies, there was a statistically significant difference in pain, as assessed by VAS scores, between the active Northstar System and the placebo treatment. This difference existed at all sites and was without significant interaction of the procedure type, venipuncture or intravenous cannulation. The results may be further strengthened by the administration of three active treatments and one placebo treatment to each subject thereby allowing them a comparison on which to base their VAS scores and thus providing greater consistency in scoring between treatments and sites.

To evaluate for clinically significant differences in the VAS scores, they were grouped to indicate little or no pain with the procedure (VAS scores ≤ 3) and severe pain (VAS scores ≥ 7). The table below shows the results of this grouping comparing procedure sites and treatment type. For each site and overall, treatment with the Northstar system resulted in more subjects experiencing little or no pain with their procedures and fewer subjects experiencing severe pain with their procedures compared to placebo.

Table 45. Comparison of Pain Levels by Treatment and Site (based on Sponsor’s Data)

Procedure Site	VAS ≤ 3		VAS ≥ 7	
	Placebo	Northstar	Placebo	Northstar
Hands	[n=24] 13 (54%)	[n=72] 59 (82%)	[n=24] 4 (17%)	[n=72] 3 (4%)
Arms	[n=23] 13 (57%)	[n=73] 70 (96%)	[n=24] 3 (13%)	[n=73] 0 (0%)
Total	[n=47] 26 (55%)	[n=145] 129 (89%)	[n=47] 7 (15%)	[n=145] 3 (2%)

In summary, this study supports the claim of efficacy for analgesia with the Northstar System.

4 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling

7 INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

Based upon analysis of the data presented and evaluation of the case report forms available at the time of this review, the following findings were made with regards to the safety of the Northstar system.

1. No deaths or serious adverse events occurred during the development and testing of this drug product.
2. A total of 1010 adult and pediatric subjects were exposed to the MIP III prototype and 168 subjects were exposed to the MIP II prototype. Many of these subjects received multiple exposures to the Northstar system. Some subjects also received placebo devices, both of the MIPs, or all three.
3. Studies were conducted with early prototypes, MIP I and the — to select the doses of lidocaine and epinephrine and the amount of electrical charge that produced analgesia with minimal side effects, e.g., dermal irritation and treatment discomfort.
4. Comparison of the Northstar system with placebo for safety findings will need to be clarified in labeling, as two types of placebos were used in the trials. One placebo was the Northstar system without current application. This placebo was not associated with any skin reactions including burns, blistering, rash and dermatitis. The other placebo was an active, i.e., current delivered, Northstar system containing no lidocaine. The sponsor used the iontophoretically delivered epinephrine to cause blanching at the placebo site and thus allow double blinding of the studies. In contrast to the passive (no current) placebo, the epinephrine-containing active placebo was associated with an incidence and pattern of skin reactions and adverse events that were similar to those of the MIP III system.
5. The most common adverse events included dermal reactions that were generally mild in severity and resolved within 24 hours. These included erythema at the patch application site and blistering/papular rash at the site of the anode.
6. Burns occurred, although rarely, at the application site. They were treated conservatively, e.g., cool compresses, and resolved without further intervention usually in less than one week. Burns that were associated with the MIP II patch lasted up to 18 days.
7. Failure of the device to deliver a full dose of medication due to "high impedance" occurred rarely, except in study 98NS 01-09, where it affected 25% of subjects. This condition has the theoretical risk of a burn injury, but this was not observed in any of the studies. The limited ability of the device to increase voltage so as to deliver the preset charge probably minimizes, if not eliminates, the risk of burn injury under high impedance conditions. In addition, the device warns of a failure to deliver the appropriate charge so corrective action can be taken.
8. Repeat applications of the Northstar system at the same site and multiple simultaneous applications of the Northstar system are events that can be readily anticipated in clinical practice but were not evaluated.

7.2 Adequacy of Exposure and Safety Assessment

Twenty-five clinical studies were conducted under IND 048,365 in which, 1724 subjects were exposed to the various configurations of the Northstar system or placebo. All of these subjects received the dose of drug, i.e., concentrations of lidocaine and epinephrine as well as current and iontophoresis time, as is found in the to-be-marketed product. The table below is reproduced from the NDA and details all of the exposures. The MIP III is the version of the Northstar system for which approval is sought. By prior agreement with the FDA, safety data for both the MIP II and the MIP III were to be considered for determination of safety of the to-be-marketed product. There were 16 studies that used the MIP III and nine other studies that were preliminary in nature and used earlier prototypes of the patch: MIP I, MIP II, or a — three studies of which used the MIP II. From these trials, the Sponsor formed an integrated safety database using data obtained from only ten of the MIP III trials and none of the MIP II studies. The Sponsor claimed that data from the other trials were not amenable to inclusion in the database and therefore, needed to be considered individually.

The studies using prototypes earlier than MIP II were considered developmental in nature and, were not considered to provide supportive information for the ISS. These nine studies were summarized generally by the sponsor.

The sponsor organized the safety analysis of the 1340 subjects of the 1347 who were randomized and treated with either the MIP III Northstar system or placebo by the general design of each study. The integrated database included the four placebo-controlled studies ($N_{\text{randomized}}=664$) and the six open-label studies ($N_{\text{randomized}}=484$). Safety data were presented separately for each of the five studies not included in the integrated format ($N_{\text{randomized}}=199$).

Two studies of the MIP III Northstar system were not included in either the integrated format or the individual study format because both were discontinued prematurely. Study BDTS-99-73 was discontinued after two subjects were enrolled because the original Sponsor, BDTS, transferred the development of the Northstar system to Vyteris, Inc. A brief summary of the safety results from this study was included for completeness. Study BDTS-99-78 was approved by the Institutional Review Board, but was canceled before any subjects were enrolled.

Nine other studies were conducted with the Northstar system. These studies were preliminary in nature and used earlier prototypes of the patch: MIP I, MIP II, or a — These studies were considered by the Sponsor to be developmental in nature and therefore, not to provide supportive information for this ISS. These nine studies were summarized generally for completeness. In this review, the data from these studies were evaluated and taken into consideration of the overall safety profile of the product.

Overall, the extent of exposure in the Phase 2/3 studies, particularly those involving the MIP III patch, appears adequate for meaningful review.

Table 52. Number of Treated Subjects by Study & Prototype (modified Table 1 from ISS, p.20)

Study	Subjects [†]	Treatment	Treatments/Subjects
MIP III	1345		
Placebo-Controlled Studies	664		
*98NS-01-10 (Phase II) ¹	49	Placebo	25/25
		MIP III Patch	24/24
*BDTS-00-16 (Phase III) ²	67	Placebo	33/33
		MIP III Patch	34/34
*BDTS-99-67 (Phase III) ²	276	Placebo	139/139
		MIP III Patch	137/137
*BDTS-99-68 (Phase III) ²	272	Placebo	136/136
		MIP III Patch	136/136
Open-Label Studies	484		
*BDTS-00-10 (Phase I)	12	MIP III Patch	36/12
*BDTS-00-11 (Phase I)	15	MIP III Patch	45/15
*BDTS-00-17 (Phase III)	89	MIP III Patch	89/89
*BDTS-00-40 (Phase I)	41	MIP III Patch	41/41
*BDTS-99-56 (Phase I)	13	MIP III Patch	39/13
*BDTS-00-57 (Surveillance)	312	MIP III Patch	312/312
BDTS-99-73 (Phase II)	2	MIP III Patch	2/2
Other Studies	197		
98NS01-09 (Phase I) ¹	61	Placebo (MIP II)	20/20
		Placebo (MIP III)	71/54
		MIP II Patch	37/37
		MIP III Patch	95/59
98NS01-11 (Phase I) ¹	48	Placebo	48/48
		MIP III Patch	144/48
BDTS-99-24 (Phase I) ²	21	Placebo	21/21
		MIP III Patch	21/21
BDTS-99-25 (Phase I) ^{1&2}	38	Placebo	49/38
		MIP III Patch	49/38
		Active Placebo	48/38
Vyteris-01-01 (Phase I)	29	MIP III Patch (lido/epi)	29/29
		MIP III (lido only)	29/29
Other Prototype	379		
95NS01-01 (Phase I)	12	Placebo	12/12
		—	84/12
95NS01-02 (Phase I)	3	Placebo	3/3
		—	21/3
95NS01-3A (Phase I)	48	Placebo	24/24
		—	72/48
95NS01-3B (Phase I)	60	Placebo	20/20
		—	100/60

Study	Subjects	Treatment	Treatments/Subjects
96NS01-04 (Phase I)	64 [‡]	Placebo	26/64
		—	32/64
		EMLA Cream	16/64
		Phenylephrine Patch	18/64
		— anode	18/64
		lower peak current	18/64
96NS01-05 (Phase I)	36	Placebo (MIP I)	18/18
		—	18/18
		MIP I Patch	18/18
		lido inf (5%)	18/18
97NS01-06 (Phase I) [†]	62	Placebo	25/25
		Placebo (MIP II)	25/25
		—	37/37
		MIP II Patch	37/37
98NS01-07 (Phase I)	80	MIP II Patch	160/80
98NS01-08 (Phase I)	14	MIP II Patch	32/14
Total	1724		

[†]includes placebo exposed subjects

[‡]subjects received two of six treatments

lido = lidocaine; epi = epinephrine; inf = infusion.

* = studies included in integrated safety database

¹Placebo = lidocaine and epinephrine patch without current

²Placebo = epinephrine patch with current

7.3 Methods for Review of Safety

The safety review consisted of a review and analyses of the Integrated Summary of Safety (ISS) database, review of the safety-related data of individual study reports and CRTs not included in the ISS, and comparison of the non-integrated and integrated safety data for discrepancies in safety findings. Comparison was also made between the safety findings of the two types of placebos used in the controlled trials, those that consisted of iontophoretically administer epinephrine and those that consisted of the Northstar system without current application. Lastly, the Sponsor's database was also used for verification analyses.

During the review process, requests for more information and questions regarding various aspects of the ISS and subject disposition were sent to the Sponsor. Those responses that were available were incorporated into the review; several are still outstanding.

7.4 Subject Demographics

The demographic characteristics for all subjects who participated in all 25 studies with the Northstar system are summarized in the table below. It was noted that in the demographics table,

the number of subjects in “Other Prototypes” studies, and therefore, the grand total of subjects are off by one compared to the numbers in **Table 52** above. In the **Table 52** above, study 98NS-01-08 is listed as having 14 subjects. Fourteen subjects were indeed randomized; however, one withdrew consent. The discrepancy does little to alter the final results, provided the veracity of the remaining data is trustworthy.

Overall, the subjects were predominantly female and Caucasian. In the placebo-controlled studies, 57.7% and 58.0% of the subjects in the placebo and Northstar treatment groups, respectively, were female, and 70.6% and 68.0% of the placebo and Northstar treatment groups, respectively, were Caucasian. In the open label studies, 62.4% of the subjects were female and 85.3% were Caucasian. In the remaining MIP III studies, 61.4% of the subjects were female and 76.1% were Caucasian. In studies conducted with other prototypes of the Northstar system, 62.5% of the subjects were female and 59.6% were Caucasian. In both the placebo and Northstar treatment groups in the placebo-controlled studies, approximately equal numbers of pediatric (≤ 17 years) and adult (≥ 18 years) subjects were enrolled. In the open-label studies, the majority of subjects were adults (78.7%). All other studies using MIP III were done in only adult subjects, and only 2 subjects (0.5%) from studies conducted using other prototypes of the Northstar system were 17 years of age or less.

Table 53. Summary of Randomized Subject Demographics (Table 5 from ISS, p.45)

Characteristic	MIP III				Other Prototypes ⁴	Total
	Placebo-Controlled Studies ¹		Open-Label Studies ²	Other Studies ³		
	Placebo (N=333)	Northstar (N=331)	Northstar (N=484)	(N=197)	(N=378)	(N=1723)
Age (n [%])						
≤ 17 yr	163 (48.9)	166 (50.2)	101 (20.9)	1 (0.5)	2 (0.5)	433 (25.1)
5-7 yr	41 (12.3)	44 (13.3)	20 (4.1)			
8-11 yr	60 (18.0)	61 (18.4)	41 (8.5)			
12-17 yr	62 (18.6)	61 (18.4)	40 (8.3)			
≥ 18 yr	170 (51.1)	165 (49.8)	381 (78.7)	196 (99.5)	374 (98.9)	1287 (74.8)
Unknown	0	0	2 (0.4)	0	2 (0.5)	2 (0.1)
Gender (n [%])						
Male	141 (42.3)	139 (42.0)	180 (37.2)	76 (38.6)	105 (27.8)	641 (37.2)
Female	192 (57.7)	192 (58.0)	302 (62.4)	121 (61.4)	236 (62.4)	1043 (60.5)
Unknown ⁵	0	0	2 (0.4)	0	37 (9.8)	39 (2.3)
Race (n [%])						
Caucasian	235 (70.6)	225 (68.0)	413 (85.3)	150 (76.1)	235 (62.2)	1258 (73.0)
Black	46 (13.8)	49 (14.8)	10 (2.1)	4 (2.0)	0	109 (6.3)
Hispanic	43 (12.9)	48 (14.5)	10 (2.1)	31 (15.7)	22 (5.8)	154 (8.9)
Asian	3 (0.9)	3 (0.9)	3 (0.6)	11 (5.6)	34 (9.0)	54 (3.1)
Other	6 (1.8)	6 (1.8)	5 (1.0)	1 (0.6)	4 (1.0)	22 (1.3)
Unknown ⁶	0	0	43 (8.9)	0	83 (22.0)	126 (7.3)

¹Placebo-controlled studies: BDTS-00-16, BDTS-99-68, BDTS-99-67, and 98NS-01-10.

²Open-label studies: BDTS-00-17, BDTS-00-57, BDTS-00-40, BDTS-00-11, BDTS-00-10, BDTS-99-56.

³Other MIP III studies: BDTS-99-25, BDTS-99-24, 98NS-01-11, 98NS-01-09, and Vyteris-01-01.

⁴Other prototype: 98NS-01-08, 98NS-01-07, 97NS-01-06, 96NS-01-05, 96NS-01-04, 95NS-01-3B, 95NS-01-3A, 95NS-01-02, and 95NS-01-01.

⁵Gender data were not collected for Study 96NS-01-05.

⁶Race data were not collected for Studies BDTS-00-40 and 98NS-01-07.

7.5 Subject Disposition

Generally, subjects received a single application of the Northstar system; however, in some studies the Northstar system was applied to several treatment sites sequentially. No summary table of extent of exposure was produced for this ISS. The table below provides the number of treatment applications and subjects for each of the different patch prototypes.

Table 54. Number of Treatments & Subjects for Each Patch Prototype (modified from Table 4 from ISS, p. 43)

Treatment	Treatments	Subjects
Placebo (—)	110	110
—	418	234
Placebo (MIP I)	18	18
MIP I Patch	18	18
Placebo (MIP II)	44	44
MIP II Patch	266	168
Placebo (MIP III)	522	494
MIP III Patch	1233	1010

The ISS describes the subjects enrolled in the Northstar system studies using the MIP III, which is the patch proposed for approval. A total of 1148 subjects were enrolled in the studies integrated into the safety analysis: 333 subjects were assigned to receive placebo and 815 subjects were assigned to receive treatment with the Northstar system. In the six studies not integrated into this safety analysis, 199 subjects were enrolled; all scheduled to receive treatment with the MIP III patch.

The table below presents subject disposition and the reasons for discontinuation for subjects who participated in the integrated placebo-controlled and open-label studies with the Northstar system. In all these studies, more than 94% of the subjects completed study treatment. In the placebo-controlled studies, 5.1% (17/333) of subjects in the placebo group and 3.9% (13/331) of

subjects in the Northstar group discontinued treatment. In the open-label studies, 2.9% (14/484) of subjects discontinued treatment.

For both placebo-treated and Northstar-treated subjects, the most common reason for discontinuation was adverse events: 2.1% (7/333) of subjects in the placebo group and 0.8% (7/815) of subjects in the Northstar group (both controlled and uncontrolled studies combined).

Table 55. Subject Disposition in the Integrated MIP III Studies (Table 6 from ISS, p.47)

Disposition	Placebo-Controlled Studies ¹		Open-Label Studies ²
	Placebo n (%)	Northstar n (%)	Northstar n (%)
Total Number of Subjects Randomized	333 (100.0)	331 (100.0)	484 (100.0)
Total Number of Subjects Who Received Study Treatment (Safety)	331 (99.4)	330 (99.7)	482 (99.6) ³
Total Number of Subjects Who Completed Study Treatment	316 (94.9)	318 (96.1)	470 (97.1)
Total Number of Subjects Who Prematurely Discontinued	17 (5.1)	13 (3.9)	14 (2.9)
Reason for Not Completing the Study:			
Technical Failure	5 (1.5)	5 (1.5)	1 (0.2)
Adverse Event	7 (2.1)	4 (1.2)	3 (0.6)
Consent Withdrawn/Refused Further Treatment	2 (0.6)	0	1 (0.2)
Protocol Violation	1 (0.3)	0	4 (0.8)
Lost to Follow-Up	2 (0.6)	2 (0.6)	0
Incomplete Delivery	0	0	2 (0.4)
Other	0	2 (0.6)	3 (0.6)

¹Placebo-controlled studies: BDTS-00-16, BDTS-99-68, BDTS-99-67, and 98NS-01-10.

²Open-label studies: BDTS-00-17, BDTS-00-57, BDTS-00-40, BDTS-00-11, BDTS-00-10, and BDTS-99-56.

³Subjects 002 and 004 in the open-label study BDTS-00-40 were discontinued before the study treatment was administered.

Note: Percentages are based on the number of subjects enrolled/randomized.

Five subjects were randomized but did not receive study drug. Two subjects in study BDTS-00-40 withdrew before administration of the Northstar system due to unsuccessful blood draws. This was consistent with the protocol requirements

7.6 Deaths

No deaths occurred in clinical studies of the Northstar system or its prototypes.

7.7 Non-Fatal Serious Adverse Events

There were no serious adverse events during any of the clinical studies of the Northstar system or its prototypes.

7.8 Adverse Events Leading to Study Discontinuation

In the placebo-controlled studies, a total of 11 (1.7%) of the subjects discontinued from the study due to an adverse event, 7 (2.1%) who were receiving treatment with placebo and 4/331 (1.2%) who were receiving treatment with the Northstar system. The adverse events resulting in discontinuation were pain NOS [2 (0.6%) placebo-treated subjects and 1 (0.3%) Northstar-treated subjects], application site burning [2 (0.6%) placebo-treated subjects and 1 (0.3%) Northstar-treated subjects], application site pain [2 (0.6%) placebo-treated subjects and 2 (0.6%) Northstar-treated subjects], and vasoconstriction [1 (0.3%) placebo-treated subject]. All of the adverse events were considered to be probably related to the study treatment. About half of the adverse events leading to discontinuation were moderate in intensity in both treatment groups (3/7 of the placebo-treated subjects, 2/4 of the Northstar-treated subjects); the rest were mild in intensity. All adverse events resolved spontaneously, usually within 24 hours, and none required intervention.

In the open-label studies, 3 (0.6%) subjects discontinued from the study due to an adverse event. Two (0.4%) of these subjects discontinued due to application site burning and 1 (0.3%) subject discontinued due to application site pain. All of these events were considered, by the Sponsor, to be probably related to study treatment, and were moderate in intensity.

Ten subjects in the placebo-controlled studies [5 (1.5%) placebo-treated subjects and 5 (1.5%) Northstar-treated subjects] and 1 subject (0.2%) in the open-label studies discontinued from study treatment due to “technical failure” (not to be confused with “high skin impedance” which was not considered an adverse event). Of the 11 technical failures, only two were confirmed as controller failures. In the remaining cases, no problems were noted with the controllers upon inspection by Vyteris. Therefore, these problems were thought to be attributable to handling errors by the investigational sites.

An overview of the adverse events that resulted in study discontinuation in all of the Northstar studies is presented in the table below.

Table 56. Adverse Events Associated with Study Discontinuation (based on Sponsor's data)

Adverse Event	Placebo	Northstar	Overall in Placebo-controlled	Overall in Open-label
Overall	7 (2.1%)	4 (1.2%)	11 (1.7%)	3 (0.6%)
pain NOS	2 (0.6%)	1 (0.3%)		
application site burning	2 (0.6%)	1 (0.3%)		2 (0.4%)
application site pain	2 (0.6%)	2 (0.6%)		1 (0.3%)
vasoconstriction	1 (0.3%)			
technical failure	5 (1.5%)	5 (1.5%)	10 (1.5%)	

7.9 Overall Evaluation of Adverse Events

7.9.1 Approach to Eliciting Adverse Events in the Development Program

In all studies, adverse events (AEs) were reported by the patient or subject and by the investigators in an ongoing manner throughout the study. An adverse event was defined as any unintended, unfavorable clinical sign, symptom, medical complaint or clinically relevant change in laboratory test value, whether or not considered to be test article related. Adverse events were characterized by type, incidence, intensity, and causality. They were graded as mild, moderate, or severe in intensity and coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary. The investigators collected adverse event information from the onset of the trials until designated protocol-established post-treatment endpoints.

Additionally, Draize scoring was used in the clinical trials to assess dermal effects, specifically, edema and erythema, after application of the Northstar system. Scoring was performed at prespecified timepoints during the trials and typically included an assessment immediately after the patch was removed and 24 hours later. A Draize score of 4 was treated as an adverse event. The Draize scoring system is shown in the table below. No subject received a Draize score of 4.

Table 57. Draize Scoring (Table 3 from BDTS-99-67 Final Study Report, p. 114)

Symptom	Description	Value
Erythema (redness)	No Erythema	0
	Very Slight Erythema—barely perceptible	1
	Well Defined Erythema	2
	Moderate to Severe Erythema	3
	Severe Erythema—beet redness to slight eschar formation (injuries in depth)	4
Edema (swelling)	No Edema	0
	Very Slight Edema—barely perceptible	1
	Well Defined Edema—edges of area well defined/raising	2
	Moderate to Severe Edema—raised approximately 1mm	3
	Severe Edema—raised more than 1mm and beyond exposed area	4

7.9.2 Appropriateness of Adverse Event Categorization and Preferred Terms

All reported adverse events were categorized by system organ class and preferred term using the MedDRA dictionary. Review of the pooled Phase 2/3 adverse event database was notable for the following.

- A distinction was made between burning and pain, either procedure related or treatment related, the former was coded as “application site burning” and the latter as “pain NOS” or post procedural pain.”
- Some burning sensations were coded as “application site burning” and others as “burns NOS.”
- Skin reactions described as “small red bumps,” “pustule,” “generalized red area,” and “skin...red with small raised bumps” were classified as “application site papules,” “application site rash,” and “rash pustular.”

Overall, these were minor points that did not preclude a detailed review of safety data.

7.9.3 Analyses and Explorations

Information in the following subsections was derived from analyses of the data contained in the ISS database. Analyses of the nine studies involving the MIP II and MIP III that were not included in the database are summarized in the last subsection.

The incidence of adverse events in each study treatment group was tabulated by intensity and attribution to study treatment. If an adverse event was reported more than once by a single subject during the study period, the greatest intensity and the worst-case attribution were tabulated. Summary tables were provided for all adverse events, intensity of adverse events, and adverse events related to the Northstar system. The incidence of adverse events was also assessed within subgroups defined according to the following baseline characteristics: age (5 to 7 years, 8 to 11 years, 12 to 17 years, 18 to 65 years, and >65 years), gender, and race (Caucasian and other). All data for subjects who received at least one application of the study treatment were included in the adverse event tables.

7.9.3.1 Incidence of Adverse Events in All Integrated Studies

An overview of the number of subjects who experienced any adverse event, any adverse event considered to be related to the Northstar system, or who were discontinued prematurely due to an adverse event is presented in the table below. Overall, similar percentages of subjects experienced an adverse event regardless of study design or treatment. A higher percentage of subjects in the open-label studies experienced an adverse event that was considered, by the Sponsor, to be possibly or probably related to Northstar system than did subjects in the placebo-controlled studies, regardless of treatment (10.0% [open-label] vs. 4.2% [placebo] and 4.8% [Northstar]). The proportion of subjects who discontinued the study due to an adverse event was

low in both the placebo-controlled studies (2.1% [placebo] and 1.2% [Northstar]) and the open-label studies (0.6%). As stated above, none of the subjects in any of the studies experienced a serious adverse event or died.

Table 58. Summary of Adverse Events (table 7 from ISS, p. 49)

	Placebo-Controlled Studies¹		Open-Label Studies²
	Placebo (N=331)	Northstar (N=330)	Northstar (N=482)
Total Number (%) of Subjects with Any Adverse Events	35 (10.6)	37 (11.2)	62 (12.9)
Total Number (%) of Subjects with Any Adverse Events Possibly or Probably Related to Study Drug/Device, as determined by Sponsor	14 (4.2)	16 (4.8)	48 (10.0)
Total Number (%) of Subjects Who Discontinued Due to Adverse Events	7 (2.1)	4 (1.2)	3 (0.6)

¹Placebo-controlled studies: BDTS-00-16, BDTS-99-68, BDTS-99-67, and 98NS-01-10.

²Open-label studies: BDTS-00-17, BDTS-00-57, BDTS-00-40, BDTS-00-11, BDTS-00-10, and BDTS-99-56.

In the open-label studies, the most frequently reported adverse event was application site papules, experienced by 40/482 (8.3%) subjects. "Application site papules" were not seen in any subject in the placebo-controlled studies, however there were reports of milia in this population. In the placebo-controlled studies, pain not otherwise specified (NOS) was the most common adverse event in both the placebo-treated and the Northstar-treated subjects. The incidence of pain NOS was higher in subjects receiving placebo (15/331 [4.5%]) than in subjects receiving treatment with the Northstar system (8/330 [2.4%]). In the adverse events text, pain NOS referred most often to "procedure pain," "post operative pain" and "pain." The table below summarizes the adverse events by body system and preferred term for the different study designs and treatment groups.

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Table 59. Adverse Events by Body System and Preferred Term (Table 8 from ISS, pp. 51 and 52)

Body System Preferred Term ³	Placebo-Controlled Studies ¹		Open-Label Studies ²
	Placebo (N=331) n (%)	Northstar (N=330) n (%)	Northstar (N=482) n (%)
Number (%) of Subjects with Any Treatment Adverse Event⁴	35 (10.6)	37 (11.2)	62 (12.9)
Cardiac Disorders	1 (0.3)	0	0
Tachycardia NOS	1 (0.3)	0	0
Gastrointestinal Disorders	3 (0.9)	4 (1.2)	0
Nausea	2 (0.6)	3 (0.9)	0
Sore Throat NOS	1 (0.3)	0	0
Vomiting NOS	0	1 (0.3)	0
General Disorders and Administration Site Conditions	24 (7.3)	16 (4.8)	54 (11.2)
Application Site Burning	2 (0.6)	1 (0.3)	2 (0.4)
Application Site Pain	4 (1.2)	3 (0.9)	1 (0.2)
Application Site Pallor/Blanching	1 (0.3)	0	0
Application Site Papules	0	0	40 (8.3)
Application Site Pruritus	0	1 (0.3)	0
Application Site Rash	0	0	1 (0.2)
Chest Pain NEC	0	1 (0.3)	0
Lethargy	1 (0.3)	0	0
Edema NOS	0	0	1 (0.2)
Pain NOS	15 (4.5)	8 (2.4)	10 (2.1)
Pyrexia	1 (0.3)	3 (0.9)	0
Infections and Infestations	2 (0.6)	0	1 (0.2)
Nasopharyngitis	1 (0.3)	0	0
Pneumonia NOS	1 (0.3)	0	0
Rash Postural	0	0	1 (0.2)
Injury and Poisoning	1 (0.3)	5 (1.5)	6 (1.2)
Burns Second Degree	0	1 (0.3)	0
Burns NOS	0	0	6 (1.2)
Subcutaneous Hematoma	1 (0.3)	3 (0.9)	0
Sunburn	0	1 (0.3)	0
Musculoskeletal, Connective Tissue and Bone Disorders	0	1 (0.3)	0
Back Pain	0	1 (0.3)	0
Neoplasms Benign and Malignant (Including Cysts and Polyps)	0	2 (0.6)	0
Barretts Esophagus	0	1 (0.3)	0
Colon Cancer NOS	0	1 (0.3)	0
Nervous System Disorders	3 (0.9)	5 (1.5)	3 (0.6)
Dizziness (Except Vertigo)	0	1 (0.3)	0
Headache NOS	2 (0.6)	2 (0.6)	1 (0.2)

Hypoesthesia	0	1 (0.3)	2 (0.4)
Vasovagal Attack	1 (0.3)	1 (0.3)	0
Psychiatric Disorders	0	1 (0.3)	0
Restlessness	0	1 (0.3)	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.3)	0
Rhinitis NOS	0	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	4 (1.2)	5 (1.5)	1 (0.2)
Dermatitis NOS	0	1 (0.3)	0
Erythema NEC	1 (0.3)	1 (0.3)	1 (0.2)
Milia	3 (0.9)	2 (0.6)	0
Pruritus NOS	0	2 (0.6)	0
Urticaria NOS	0	1 (0.3)	0
Surgical and Medical Procedures	0	1 (0.3)	0
Post Procedural Pain	0	1 (0.3)	0
Vascular Disorders	2 (0.6)	5 (1.5)	0
Hypertension NOS	0	1 (0.3)	0
Vascular Disorder NOS	0	1 (0.3)	0
Vasoconstriction	2 (0.6)	3 (0.9)	0

¹Placebo-controlled studies: BDTS-00-16, BDTS-99-68, BDTS-99-67, and 98NS-01-10.

²Open-label studies: BDTS-00-17, BDTS-00-57, BDTS-00-40, BDTS-00-11, BDTS-00-10, and BDTS-99-56.

³The MedDRA dictionary was used for coding.

⁴If a subject experienced more than one adverse event within a category, the subject was counted once under that category.

NOS=not otherwise specified; NEC=not elsewhere classified.

Additionally, when the incidence rate of adverse events was stratified by age, similar distributions were observed between placebo and Northstar treatment in the placebo-controlled studies and among the subject age groups in the open-label studies. In the open-label studies, pediatric subjects (<18 years of age) had a higher incidence of application site papules (31/101, 30.7%) than did subjects 18 to 64 years of age (6/264, 2.3%) or subjects ≥65 years of age (3/117, 2.6%).

Due to the predominance of Caucasians in both the placebo-controlled and open-label studies, it was not possible to do subgroup analyses of the incidence of adverse events for each of the separate race groups. However, the incidence of adverse events in Caucasian subjects was similar between subjects receiving placebo-treatment (11.5%, 27/234) and those receiving Northstar-treatment (12.1%, 27/224) in the placebo-controlled trials. The incidence of adverse events was also similar for subjects of all other races, 8.2% (8/97) for placebo-treated subjects and 9.4% (10/106) for Northstar-treated subjects. In the open-label studies, the incidence of adverse events was 14.3% (59/413) for Caucasian subjects and 4.3% (3/69) for subjects of all other races.

Subgroup analyses were also done to compare the incidence of adverse events between males and females. In the placebo-controlled studies, the incidence of adverse events was 8.6%

(12/139) for placebo-treated male subjects, 9.4% (13/138) for Northstar-treated male subjects, 12.0% (23/192) for placebo-treated female subjects, and 12.5% (24/192) for Northstar-treated female subjects. The incidence of adverse events was 16.1% (29/180) for male subjects and 10.9% (33/302) for female subjects in the open-label studies.

7.9.3.2 Incidence of Treatment-Related Adverse Events in All Integrated Studies

In the Sponsor's analysis, more subjects in the open-label studies experienced an adverse event that was considered to be possibly or probably related to the study treatment than did subjects in either treatment group in the placebo-controlled studies (10.0% vs. 4.2% [placebo] and 4.8% [Northstar], respectively). The most frequently reported treatment-related adverse event was application site papules and this event was only reported by subjects in the open-label Northstar system studies (36/482[7.5%] subjects). Aside from this event, the only treatment-related adverse event experienced by more than 1% of subjects in the open-label studies was burns NOS (1.2%). All treatment-related adverse events in the placebo-controlled studies were experienced by less than 1% of the subjects in each treatment group. The table below summarizes the treatment-related adverse events by body system and preferred term for the different study designs and treatment groups.

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Table 60. Adverse Events Possibly/Probably Related to Study Drug by Body System and Preferred Term (Table 9 from ISS, p. 54)

Body System Preferred Term ³	Placebo-Controlled Studies ¹		Open-Label Studies ²
	Placebo (N=331)	Northstar (N=330)	Northstar (N=482)
	n (%)	n (%)	n (%)
Number (%) of Subjects with Any Treatment-Related⁴ Adverse Event⁵	14 (4.2)	16 (4.8)	48 (10.0)
General Disorders and Administration Site Conditions	9 (2.7)	5 (1.5)	41 (8.5)
Application Site Burning	2 (0.6)	1 (0.3)	2 (0.4)
Application Site Pain	4 (1.2)	3 (0.9)	1 (0.2)
Application Site Pallor/Blanching	1 (0.3)	0	0
Application Site Papules	0	0	36 (7.5)
Application Site Pruritus	0	1 (0.3)	1 (0.2)
Edema NOS	0	0	1 (0.2)
Pain NOS	2 (0.6)	1 (0.3)	0
Infections and Infestations	0	0	1 (0.2)
Rash Pustular	0	0	1 (0.2)
Injury and Poisoning	1 (0.3)	4 (1.2)	6 (1.2)
Burns NOS	0	0	6 (1.2)
Burns Second Degree	0	1 (0.3)	0
Subcutaneous Hematoma	1 (0.3)	3 (0.9)	0
Nervous System Disorders	0	1 (0.3)	1 (0.2)
Dizziness (Except Vertigo)	0	1 (0.3)	0
Hypoesthesia	0	0	1 (0.2)
Skin and Subcutaneous Tissue Disorders	3 (0.9)	3 (0.9)	1 (0.2)
Erythema NEC	1 (0.3)	1 (0.3)	1 (0.2)
Milia	2 (0.6)	2 (0.6)	0
Pruritus NOS	0	1 (0.3)	0
Urticaria NOS	0	1 (0.3)	0
Vascular Disorders	1 (0.3)	3 (0.9)	0
Vasoconstriction	1 (0.3)	3 (0.9)	0

¹Placebo-controlled studies: BDTS-00-16, BDTS-99-68, BDTS-99-67, and 98NS-01-10.

²Open-label studies: BDTS-00-17, BDTS-00-57, BDTS-00-40, BDTS-00-11, BDTS-00-10, and BDTS-99-56.

³The MedDRA dictionary was used for coding.

⁴Related to study drug or device was defined as possibly or probably related.

⁵If a subject experienced more than one adverse event within a category, the subject was counted once under that category.

NOS=not otherwise specified; NEC=not elsewhere classified.

7.9.3.3 Incidence of Adverse Events by Maximum Intensity in All Integrated Studies

Overall, most of the adverse events reported in the studies were mild or moderate in intensity. A total of 6 subjects who were treated with the Northstar system, (5 [1.5%] subjects in the placebo-controlled and 1 [0.2%] subject in the open-label studies), experienced an adverse event (pain NOS) that was considered to be severe in nature. The pain typically lasted no more than several minutes. From the adverse events table in the ISS, three episodes of severe pain were from the procedure and lasted less than 2 minutes, two episodes were simply described as “pain” and had no duration time recorded, and one episode of “post-operative pain” was graded as severe but had no duration time associated with it. Overall, 33 subjects had episodes of “pain NOS.” Of these 33, nineteen were described as having pain with their procedure, nine were listed as only “pain” and five were listed as having post-operative pain. All episodes of pain lasted less than an hour when the durations were recorded, but four episodes of “pain” and three of post-operative pain had no durations recorded.

No placebo-treated subject experienced an adverse event considered severe in intensity.

7.9.3.4 Summary of Dermal Effects for Edema and Erythema in All Integrated Studies

Greater than 85% of subjects in all the Northstar studies did not experience edema within 10 minutes after patch removal or 24 hours after treatment as assessed by Draize scoring (refer to **Table 57** for Draize scales). None of the subjects had edema that was considered severe in intensity. Predominantly, subjects experienced edema at the cathode site within 10 minutes after patch removal. Pediatric subjects appeared to be more prone to edema than adults. No subject who experienced edema had a Draize score greater than 2. For all subjects, the edema resolved spontaneously within 24 hours.

Although the majority (>80%) of subjects in all the Northstar studies experienced some degree of erythema within 10 minutes after patch removal at the cathode site, the erythema was transient and resolved for the majority of subjects within 24 hours. In study BDTS-00-11, one-third of patients (5/15) were found to have very slight erythema at 48 hours and 7% (1/15) still had well defined erythema at that time as well. In the placebo-controlled studies, elderly subjects (≥65 years) had a lower incidence rate of erythema compared with the overall subject population, while pediatric subjects appeared to be more prone to erythema. None of the subjects had erythema that was considered severe in intensity, i.e., a Draize score of 4. For all subjects the erythema resolved spontaneously, although it was noted to recur in some individuals after brief periods of resolution during the course of 24 hours following treatment.

The table below summarizes the Draize score data at the first evaluation following treatment, i.e., at 10 to 15 minutes after patch removal, and the combined scores for all evaluation times – ranging from 2.9 to 48 hours following patch application. The placebo and Northstar patches are nearly indistinguishable in terms of both erythema and edema seen immediately after treatment and over the ensuing 24 to 48 hours.

Table 61. Summary of Draize Score Data (based on Sponsor's data table)

Draize Score	First evaluation after treatment				All times combined			
	Placebo		Northstar		Placebo		Northstar	
	n	%	n	%	n	%	n	%
Erythema								
not measured	2	0.6	3	0.3	3	0.5	6	0.3
0	58	17	170	20	366	56	999	56
1	162	49	438	51	175	27	512	29
2	110	33	243	28	112	17	268	15
3	1	0.3	8	1	1	0.2	10	0.6
4	0	0	0	0	0	0	0	0
Edema								
not measured	2	0.6	4	0.5	3	0.5	7	0.4
0	285	86	756	88	608	93	1682	94
1	39	12	92	11	39	6	96	5
2	7	2	10	1	7	1	10	0.6
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0

7.9.3.5 Overall Incidence of Adverse Events

There is a degree of discretion allowed for the description of adverse events that may produce multiple terms for the same event. In the case of the Northstar system, it is not readily apparent how burns were distinguished from erythema with concomitant edema or from papular rash or from rash at patch site. In an effort to present the worst case scenario, like terms have been combined and an overall incidence determined based on number of subjects exposed and the number of treatments administered. Some patients had more than one adverse event associated with one patch application or adverse events associated with different applications; each was counted as an unique event. The categories combined formed two groups:

- Pain – including application site pain, procedure pain, burning sensation, application site burning
- Dermal irritation – including rash, papular rash, papules, milia, burns, erythema, edema

Table 62. Worst Case Scenario for Incidence of Adverse Events

Adverse Event Category	Total Incidence/ Total Population n = 1148	Placebo Incidence/ Placebo Population n = 333	Placebo Incidence/ Placebo Treatment n = 333	Northstar Incidence/ Northstar Population n = 815	Northstar Incidence/ Northstar Treatment n = 893
Patch related pain n (%)	47 (4)	21 (6)	21 (6)	26 (3)	26 (3)
Dermal irritation n (%)	60 (5)	4 (1)	4 (1)	56 (7)	56 (6)

This analysis indicates that overall less pain was associated with the use of the Northstar system than with the placebo, but that considerably more dermal reactions occurred with the Northstar

system than with placebo. The significance, if any, of the application site papules occurring in two open-label studies, 4 in BDTS-00-10 and 36 in BDTS-00-57, is unclear.

7.9.3.6 Studies of Repeat Application Effects and Dermal Irritation and Sensitization

One trial, BDTS-00-11, was conducted to determine the effects of repeat applications of the Northstar system at the same site, and one trial, BDTS-00-57, was designed specifically to evaluate dermal effects of the patch on normal skin, however, nearly all studies conducted with the MIP II and MIP III evaluated erythema and edema associated with patch use. These trials are reviewed below. A study of sensitization and irritation was not conducted and will be required as a Phase IV commitment.

7.9.3.6.1 BDTS-00-11 Evaluation of Dermal Effects After Repeat Application of the Northstar Lidocaine Iontophoretic Drug Delivery System

This was a single-center, randomized, repeat-application, Phase I clinical trial designed to assess the local response to multiple applications of the Northstar System at the same site. The study was conducted from May 1, 2000 until May 15, 2000.

7.9.3.6.1.1 Objectives

The primary objective of this study was to assess local (dermal) response to multiple applications of the Northstar System over the same anatomic site in adult subjects. The secondary objective of this study was to assess safety of multiple applications of the Northstar System over the same anatomic site.

7.9.3.6.1.2 Methods

Fifteen adult volunteers (80% male; 93% Caucasian) were treated with the Northstar system according to the draft instructions for use. Test areas were one of the following on each subject: upper chest, upper back, dorsum of the hand or antecubital fossae. Each subject was tested in a single region. The system was applied to the designated site (chosen by the site staff based on areas of skin lacking abnormalities and excessive hair), and treatment initiated. After the full iontophoretic treatment cycle was completed, the system was removed.

Three hours after the first application, a second system was applied directly over the original site. After the full iontophoretic treatment cycle was completed, the system was removed. Six hours after the initial application, a third system was applied to the original site, the treatment was delivered and the system removed. A clinician trained in Draize evaluations observed the skin at the test area immediately before and shortly after each of three Northstar treatments. Additionally each skin site was evaluated one and two days later. Specifically, assessments were made at:

T = -15 minutes (prior to T = 0: first activation of a Northstar system)

T = 15 minutes

T = 2.9 hours

T = 3.5 hours

T = 5.9 hours

T = 6.5 hours

T = 24 – 27 hours, and

T = 48 – 51 hours.

Each subject received all treatments at a single visit, and was assessed for adverse events and dermal effects at visits approximately 24 and 48 hours after the first. As per the protocol, any subject who had a Draize score that was > 2 at 48 hours would be assessed for further follow-up.

7.9.3.6.1.3 Results

Evaluation of erythema revealed 2 (13%) of the subjects had severe erythema (Draize score = 3) 15 minutes following treatment. Both incidents occurred on the antecubital fossae. At 3.5 hours following treatment, one subject continued to have severe erythema, although there were no reports of this degree of erythema at 2.9 hours after treatment. Similarly, there was again a report of severe erythema at 6.5 hours after treatment; all in the same subject. Well-defined erythema (Draize score = 2) was noted overall in 73% of subjects immediately following treatment. Although there were intervals where nothing greater than very slight erythema (Draize score = 1, barely perceptible) was reported at 2.9 and 5.9 hours after treatment, 73% of subjects were reported to have a Draize score of 2 at 6.5 hours. One subject had a Draize score of 2 at the 48-hour follow-up visit, however the investigator determined he was not in need of further evaluation. There was no proclivity for the erythema to occur at a particular site, however, subjects who exhibited erythema at one time point were most likely to do so at several.

No subject exhibited anything more than very slight edema, Draize score = 1, and that was fully resolved by 24 hours following the treatment.

No subjects withdrew from the study. During active treatment, one subject, a 45-year old male, experienced mild paresthesia in the fingers on the arm where the patch was applied. The condition resolved spontaneously within 10 minutes after the system completed delivery.

7.9.3.6.2 BDTs-00-57 Safety Surveillance Evaluation of the Northstar Iontophoretic Lidocaine Drug Delivery System

This was an open-label, randomized, single-application, single-center, prospective, Phase II study in healthy volunteers that was designed to evaluate the safety of the Northstar System and the ability of clinicians to comply with proposed instructions for use. This trial was conducted between October 24, 2000 and October 26, 2000.

7.9.3.6.2.1 Objectives

The primary objective of this study was to evaluate the safety of Northstar in terms of erythema and edema produced by its application. The secondary objective was the preliminary evaluation of the draft "Instructions For Use."

7.9.3.6.2.2 Methods

This was strictly a safety study in healthy pediatric (ages 5 years and older), adult, and geriatric subjects. Subjects were randomly assigned to receive one patch application at 1 of 4 application sites: upper chest, upper back, dorsum of the hand, and antecubital fossae. A Clinician, trained in Draize evaluation, used Draize scores to rate the test area, at 30 minutes and 24 hours ($\pm$ 8 hours) after the start of the Northstar controller. Subjects were assessed for adverse events (AEs) immediately after patch removal, at 30 minutes after the start of the controller, and approximately 24 hours ($\pm$ 8 hours) after patch application. Up to five Clinicians applied the Northstar patch treatments, and their ability to comply with the draft "Instructions for Use" was assessed.

7.9.3.6.2.3 Results

The majority of subjects experienced no edema after treatment with the Northstar system, 99.4% at the anode both 30 minutes and 24 hours after treatment, and at the cathode, 84.9% at 30 minutes following treatment and 100% the following day. No subject had a Draize score greater than 2 for edema (well-defined edema) at any time during the study.

The majority of subjects experienced no erythema at the anode site after treatment with the Northstar system, and only transient erythema was observed at the cathode site. No difference in Draize score with respect to the treatment site was observed.

Nearly 15% percent of subjects (46/312) experienced treatment-emergent AEs during the clinical trial. All of these events were described as mild or moderate in intensity. Papules at the treatment site were the most common treatment-emergent AE (37/312, 11.9%), and the treatment site most affected was the dorsum (17/79, 21.5%). All events involving papules were considered by the Investigator to be of mild intensity and possibly or probably related to treatment with the Northstar system.

Three subjects (children) discontinued from the study due to treatment-related AEs; two children reported a burning sensation and one child reported pain at the treatment site. More children (5 to 18 years) reported AEs than subjects in the other age groups, and papules were more frequently reported among children than among adults.

The preliminary evaluation of the draft "Instructions For Use" showed that approximately twice as many subjects treated by Clinicians 2 and 3 reported AEs than subjects treated by Clinician 1.

7.9.3.7 Studies Not Included in the ISS Database

Five studies involving the MIP III and three studies involving the MIP II were conducted but did not have their results included in the ISS database. The table below summarizes the essential findings in these studies. The information was obtained by review of all the datasets presented by the Sponsor. It was noted that some adverse events were not included in the adverse events tables but were reported elsewhere in the study reports such as tables of dermatological findings. This issue was raised with the Sponsor on July 10, 2003 when it was discovered that subject 98NS01-09-001-923 in study 98NS 01-09 was noted as having "adhesive from the patch remove some skin" at all four application sites. This information was found in the "DERMAL" dataset, which indicated photos were taken of the injuries. The information did not appear in the adverse event table of the data set, and it was not mentioned in the Safety Results section of the Integrated Clinical and Statistical Report.

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Table 63. Safety Findings from Non-Integrated Studies Using MIP II and MIP III Patches.

Study	MIP	No. of Subjects Enrolled	No. of Subjects Evaluated for Safety	No. Tx'd. w/ North star	Significant Safety Findings	Duration of Findings
Vyteris 01-01	III	29	29	29	none	N/A
BDTS 99-24	III	21	20	21	none	N/A
BDTS 99-25	III	38	38	36	4 burns	1-7 days
					15 cases of irritation at patch site	< 1 day
					1 dermatitis at patch site	9 days
98NS 01-09	III	61	61	61	16 subjects withdrawn for "high impedance"	N/A
					1 burn	unknown
					4 patch adhesive removed skin (all 4 sites on same 23yr. old subject)	unknown (Photos were taken. Sponsor to submit them for review.)
98NS 01-11	III	48	48	48	6 instances of blistering	< 1 hour
BDTS 99-73	III	2	2	2	none	N/A
97NS 01-06	II	62	62	61	1 burn	1 day
98NS 01-07	II	85	80	80	5 withdrawal for "technical failures" 3 were "high impedance"	N/A
98NS 01-08	II	22	13	13	6 withdrawn due to "high impedance"	N/A
					2 burns	12 – 18 days
					8 cases of purpura	3-10 days

These studies resulted in an additional 353 subjects for safety evaluation. Demographically, these studies did not differ from the other adult studies. Overall, there were 42 instances of dermatological injury. This is not considerably higher than that which occurred in the safety analysis database population when the number of treatments with the Northstar system is taken into account. Several of these studies involved multiple treatments at different sites.

7.9.4 Laboratory Findings

7.9.4.1 Electrocardiograms

Two studies completed during the Northstar clinical development program included ECG recordings as a safety evaluation: Studies 98NS-01-08 and Vyteris-01-01. Study 98NS-01-08 was a pharmacokinetic study that evaluated the concentrations of lidocaine following two applications with the MIP II patch. This study had a second part added to the study to re-evaluate the lidocaine levels in 3 subjects who had high levels during the first part of the study. ECGs were recorded during this second part of the study at the screening visit and then at 1 to 3 hours following treatment. There were no clinically significant changes to ECGs noted in any of the three subjects.

Study Vyteris-01-01 was designed to evaluate the effect of inclusion of epinephrine in the MIP III patch. Two treatments, treatment with a patch containing 10% lidocaine and 0.1% epinephrine and treatment with a patch containing 10% lidocaine only, were given to subjects on the same day separated by a recovery interval of 2 hours followed by one hour of being in a supine position in a darkened room away from stimuli. Electrocardiograms were recorded at 30 and 15 minutes before and at 10, 30, and 60 minutes following each treatment. As can be seen in the table below, there were no notable differences between the two treatments in the percentage of abnormal ECGs at any timepoint. In addition, the percentage of abnormal ECGs did not change following treatment with either patch system.

Table 64. Summary ECG Findings from Study Vyteris-01-01 (Table 29 from ISS, p. 94)

Treatment System	Parameter	ECG Diagnosis Minutes After Patch Application				
		-30	-15	10	30	60
Northstar (N = 29)	Total Normal	18	16	18	18	18
	Total Abnormal	11	13	11	11	11
	Percent Abnormal	37.9	44.8	37.9	37.9	37.9
Lidocaine Alone (N = 29)	Total Normal	16	16	16	18	20
	Total Abnormal	13	13	13	11	9
	Percent Abnormal	44.8	44.8	44.8	37.9	31.0

Two subjects had abnormal ECG recordings that were reported as adverse events, none of these events was considered related to study treatment. One subject who had abnormal transaminase values at baseline (AST value of 65 U/L and an ALT value of 53 U/L) developed a transient S₁-Q₃-T₃ pattern (possibly right ventricular strain) with a new leftward deviation of the QRS axis, which initially emerged 60 minutes after treatment with the Northstar system. This pattern persisted through the next ECG that was performed 1 hour 27 minutes later, but then reverted to the baseline pattern before treatment with the MIP III patch containing only lidocaine 15 minutes later. This subject had no other clinical abnormalities associated with this change in ECG pattern,

and the following four ECGs were normal. The subject's systolic blood pressure only increased from 104 mmHg to 110 mmHg with no associated symptoms. A second subject had an abnormal QRS complex recorded following treatment with the lidocaine only patch; however, this subject also had an abnormal ECG at baseline that was considered unlikely to have any effect on the outcome of the study.

Analysis of the ECG findings is limited in that the specific abnormalities, except for those provided above, were not included in the study reports. Rather, comments such as "ECG Abnormality is N/S per source" or "all ECGs have significant abnormalities, which were present at baseline" were listed under "ECG Finding" for the Vyteris-01-01 data in Appendix 14.2 of the Study Report.

7.9.4.2 Vital Signs

In order to partially address safety concerns regarding the addition of epinephrine to lidocaine contained within the MIP III patch, vital sign data were collected. Specifically, vital sign assessments were collected both before and after the IV cannulation or venipuncture procedure in nine of the 25 clinical studies conducted using the Northstar system. Of these, three studies were with earlier prototypes of the patch (95NS-01-02, 96NS-01-04, and 96NS-01-05). Clinical study reports from these three studies state that there were no clinically meaningful or notable changes in vital signs. The remaining six studies were done using the MIP III patch. Vital sign data from the 98NS-01-10 study were collected approximately 24 hours after application of the patch and therefore, are not likely to give any meaningful information regarding the safety of epinephrine in the patch. Vital sign data from four studies (BDTS-99-67, BDTS-99-68, BDTS-00-16, and BDTS-00-17) were collected within 10 minutes of removal of the patch and are discussed below. Even in these studies, detection of clinically significant changes in heart rate and blood pressure due to systemic absorption of epinephrine might go undetected due to the short half-life of the drug.

In all of these studies, the placebo patch contained 0.1% epinephrine. An additional study (Vyteris-01-01) evaluated vital sign data from subjects following treatment with either the Northstar system or a MIP III patch containing lidocaine only.

The table below presents a summary of vital sign data from the four Phase III studies. In all studies, both mean and median changes in vital sign data from baseline to post-treatment were negligible and clinically insignificant. Twenty percent or fewer of subjects had post-treatment changes in systolic blood pressure that were 15 mmHg or greater or changes in diastolic blood pressure that were 10 mmHg or greater, and according to the Sponsor, these were unassociated with systemic symptoms (adverse events) in over 80% of these patients. No mention was made of the other 20%, however inspection of the adverse events table indicates the following events that may be associated with changes in heart rate or blood pressure: 5 episodes of headache, 5 episodes of nausea, 2 vasovagal episodes, 1 case of hypertension, 1 case of tachycardia, 1 episode of restlessness, 1 episode of lethargy, 1 case of "vasoconstriction" described below, and an episode of sternal chest pain in a patient undergoing EGD and which was treated with Tylenol®. Inspection of all the individual subject's blood pressure and heart rate data in these

studies revealed no changes that would be considered clinically significant for patients undergoing vascular access procedures. More often blood pressure and/or heart rate decreased following treatment suggesting perhaps less apprehension on the part of the subject, but arguing against a hemodynamic effect by absorbed epinephrine. One subject in the BDTS-99-68 pediatric study had a systemic adverse event described as “vasoconstriction” that required no treatment. Specifically, the subject’s heart rate increased from 72 to 88 beats per minute, systolic blood pressure increased from 103 to 106 mmHg, and diastolic blood pressure increased from 60 to 76 mmHg, baseline to post-treatment.

Table 65. Changes in Vital Sign Measurements with Treatment (Table 27 from ISS, p.91)

Vital Sign Parameter	BDTS-99-68		BDTS-99-67		BDTS-00-16		BDTS-00-17
	Placebo	NS	Placebo	NS	Placebo	NS	NS¹
Number of Subjects²	122	124	137	134	32	34	88
Systolic BP (mmHg)							
Mean change	0.6	-0.5	-1.5	-1.9	-1.4	-0.8	2
Median change	0	0	0	0	-2	-2	1.5
Diastolic BP (mmHg)							
Mean change	0.5	0.1	-0.7	-0.8	1.1	-0.9	0.2
Median change	1	0	0	0	0	0	0
Heart Rate (bpm)							
Mean change	0.9	0.3	-0.7	-0.1	1.2	-2.8	-1.2
Median change	2	0	0	0	0	-3	0
N (SBP≥15 mmHg or DBP≥10 mmHg)³	24	25	15	10	6	5	13
Number of Subjects with AEs	3	5	2	3	2	1	1
Number of Subjects with Systemic AEs	1	4	1	0	0	0	0

¹BDTS-00-17 was open-label and had no placebo group.

²Number of subjects with both pre- and post-procedural vital sign data.

³Number of subjects with changes in SBP ≥15 mmHg or DBP ≥10 mmHg.

NS=Northstar system, BP=blood pressure, SBP=systolic BP, DBP=diastolic BP, bpm=beats per minute.

A summary of the vital sign data from Study Vyteris-01-01 is provided in the table below. There were no clinically important changes in mean vital signs observed after the application of either the Northstar system or the MIP III patch containing only lidocaine. In addition, there were no notable differences in vital signs seen in individual subjects following treatment with either the Northstar system or the patch containing only lidocaine at any timepoint. Therefore, the

inclusion of 0.1% epinephrine in the patch did not appear to have any meaningful effects on vital sign measurements, at least at the timepoints observed.

Table 66. Summary of Vital Sign Data from Study Vyteris-01-01 (Table 28 from ISS, p. 92)

Time Point (minutes)	Treatment System (N = 29)	Mean Value $\pm$ Standard Deviation			
		Blood Pressure (mmHg)		Heart Rate (beats/minute)	Respiration (breaths/minute)
		Systolic	Diastolic		
-30	Northstar	114.8 $\pm$ 8.8	72.5 $\pm$ 7.2	66.1 $\pm$ 7.6	17.6 $\pm$ 1.7
	Lidocaine Alone	114.1 $\pm$ 8.2	71.2 $\pm$ 6.3	64.5 $\pm$ 7.2	17.4 $\pm$ 1.5
-15	Northstar	113.9 $\pm$ 8.8	72.2 $\pm$ 7.1	64.3 $\pm$ 7.2	17.8 $\pm$ 1.3
	Lidocaine Alone	113.8 $\pm$ 9.1	70.9 $\pm$ 6.7	63.5 $\pm$ 9.3	17.1 $\pm$ 1.4
10	Northstar	112.7 $\pm$ 9.8	71.5 $\pm$ 7.6	64.3 $\pm$ 8.3	17.4 $\pm$ 1.6
	Lidocaine Alone	111.5 $\pm$ 10.7	71.5 $\pm$ 8.6	64.3 $\pm$ 7.2	17.0 $\pm$ 1.4
30	Northstar	115.0 $\pm$ 12.5	73.0 $\pm$ 10.0	66.2 $\pm$ 9.2	17.8 $\pm$ 1.9
	Lidocaine Alone	113.5 $\pm$ 13.6	71.7 $\pm$ 9.8	64.2 $\pm$ 8.2	16.8 $\pm$ 1.4
60	Northstar	115.5 $\pm$ 14.4	73.9 $\pm$ 8.9	66.4 $\pm$ 6.1	17.9 $\pm$ 1.0
	Lidocaine Alone	114.2 $\pm$ 9.5	73.6 $\pm$ 9.0	67.5 $\pm$ 7.8	17.5 $\pm$ 1.3

Note: Time points are relative to the start of treatment (t = 0).

The question may be raised as to whether vital sign measurements taken 10 minutes after an iontophoretic treatment will provide useful information in terms of detecting epinephrine-induced perturbations. Measurement of plasma epinephrine concentration revealed no significant change from baseline when measured 10, 30 and 60 minutes following iontophoretic treatment. As there was no evidence to suggest a rise in epinephrine levels, and there are no grounds to postulate a sudden change in plasma concentrations following iontophoresis, there appears to be no basis for speculation that vital sign perturbations would not be captured under this protocol.

7.9.4.3 Laboratory Findings

No blood chemistry or hematology assays and no urinalysis studies were performed during the development of the Northstar system. Studies were conducted however, to measure plasma concentrations of epinephrine and lidocaine.

Overall, three studies were conducted to assay plasma levels of lidocaine following application of one or more, in sequential fashion, Northstar system patches. In each study, the lidocaine concentrations were less than the level of quantitation for all but five samples. In the samples where detectable lidocaine concentrations were measured, the levels ranged from 8.88 ng/mL to 4.1 mcg/mL. The four samples with the highest levels of lidocaine were drawn either from a

“contaminated site,” i.e., where the patch had been applied (n=2), or in violation of the protocol for sampling site (n=2). A small study demonstrated the contamination of samples when taken from application sites.

One study assayed plasma epinephrine concentrations for the Northstar system and a patch containing lidocaine only. There were no measured levels that were above the normal range of epinephrine, i.e., 10 – 50 pg/mL, and no notable shifts in epinephrine levels between the placebo patch and the active system. Summary methods and results of all of these studies are provided below.

Study BDTS-99-56 evaluated plasma lidocaine concentrations before and after the sequential application of three MIP III patches on 13 subjects. Before the first application of the Northstar patch, a plasma lidocaine level was assayed. After the application, plasma lidocaine was assayed at five timepoints. ANOVA is used to determine whether plasma lidocaine levels changed over time. A Northstar was applied a second time approximately three hours after the first application, and a plasma lidocaine level was assayed. The third application of Northstar was performed thirty minutes after the second patch application, and then plasma samples were assayed at five more time points. The data from post-second application samples was used to determine what effects if any exist for “repeat” applications of the Northstar system. 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 in fact 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 was considered statistically significant.

Assay results were below the minimum level of quantitation (5 ng/mL) for all samples.

Study BDTS-00-10 also assayed lidocaine levels in 12 subjects following three applications of the MIP III patch as in BDTS-09-56.

Assay results for the majority of samples were below the minimum level of quantitation (5 ng/mL) except for two events: (1) at Baseline, subject ID 009 was measured as “<10” (insufficient volume of sample), and (2) at T225, subject ID 007 was measured as “ ” (ng/mL).

Study 98NS-01-08 assayed plasma lidocaine levels in 19 subjects receiving two patch applications one-half hour apart on opposite hands. A second part of this protocol was to demonstrate in three subjects whether or not detectable levels of lidocaine are found in blood samples drawn from the patch application site versus a site distal from the patch application, indicating that there is no systemic absorption of lidocaine.

In the Initial Part of the study, a total of 91 plasma samples were analyzed for the concentration of lidocaine. All concentrations of lidocaine obtained during the study were below the level of assay sensitivity with the exception of four samples. For Subject #006, the lidocaine concentration of the 3-h sample was reported as 0.2 µg/mL. For Subject #010, the 0.92-h (55-min) sample was reported as 0.1 µg/mL, the 1.5-h sample was reported as 0.1 µg/mL, and the 3-h sample was reported as 0.1 µg/mL lidocaine. These results were explained by the fact that because of poor venous access in the antecubital area, these samples were obtained from the back of the hand (dorsum) in violation of the protocol. The concentrations for all other times for Subjects #006 and #010 were below the level of assay sensitivity for lidocaine. The data for Subjects #006 and #010 indicated that the lidocaine concentrations obtained were contaminated. 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 these subjects showed concentrations above the level of assay sensitivity of the lidocaine assay.

In the Second Part of the study, a total of 23 plasma samples were analyzed for the concentration of lidocaine. Detectable concentrations of lidocaine were found in blood samples drawn from the patch treatment sites due to dermal contamination. No detectable concentrations of lidocaine were found in blood samples drawn from a site distal from the patch treatment (antecubital) area.

Study Vyteris-01-01 assayed plasma epinephrine levels in 29 subjects. Each subject received treatment with both the Northstar and Lidocaine Alone systems at a single visit. A total of two patches were applied to each subject, one to the dorsum of the hand and one to the antecubital fossa in the arm opposite the arm from which blood samples were drawn. The patches were applied at least 3 hours apart with subjects resting supine in a darkened room away from stimuli for at least 60 minutes prior to each patch application. Ten blood samples were drawn from the IV access device placed in the antecubital fossa of each subject and analyzed for plasma epinephrine concentrations with a minimum detection limit of 10 pg/mL. These samples were drawn at times $t = -30$ minutes (prior to application), $t = -15$ minutes, $t = 10$ minutes (immediately post-treatment), $t = 30$ minutes, and $t = 60$ minutes before and after each treatment. The number of subjects with epinephrine values shifting from baseline to maximal post-treatment values for three categories: <10 pg/mL, 10 pg/mL to 50 pg/mL, and >50 pg/mL were tabulated.

There were no subjects who had epinephrine levels that were >50 pg/mL (above the normal range) during the course of the study. None of the subjects had a clinically important increase in epinephrine levels following treatment with either the Northstar system or the Lidocaine Alone system. In addition, there were no notable differences in the maximal changes from the pre-treatment values of epinephrine between the Northstar and Lidocaine Alone systems. 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.

There were no notable differences in the shift values for epinephrine levels between the Northstar and Lidocaine Alone systems. After treatment with the Northstar and Lidocaine Alone

systems, respectively, 19 (65.5%) subjects versus 20 (70.0%) subjects had no shift in epinephrine values.

Therefore, the presence of epinephrine in the Northstar system was determined to have no effect on the systemic epinephrine levels of the subjects.

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ON ORIGINAL**

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ON ORIGINAL**

8 USE IN SPECIAL POPULATIONS

8.1 Adequacy of By-Gender Investigation and Analyses

The sponsor has included adequate numbers of subjects and patients of both genders in the clinical development program. The Sponsor has also performed adequate by-gender analyses for both the efficacy data and the safety data. Demographically, it was noted that overall, the subjects were predominantly female and Caucasian.

8.2 Elderly Population

A total of 163 subjects 65 years of age and older participated in the trials included in the safety analysis dataset. They comprised 14% of the subjects evaluable for safety. Of these, 139 subjects received treatment with the Northstar system; 17% of all Northstar treated subjects. The ages ranged from 65 to 100 years old. There were 58 subjects ages 75 years and older. Of these, 44 were treated with the Northstar system. Therefore, a sufficient range and number of elderly subjects was included in evaluation of safety and efficacy to allow appropriate labeling of use in this population.

8.3 Pediatric Population

A total of 430 subjects/patients ages 5 to 17 years old participated in the trials included in the ISS dataset. This group comprised 37% of the subjects evaluable for safety. Of these, 267 subjects/patients received treatment with the Northstar system; 33% of all Northstar treated subjects. Within the studies, the pediatric population was often subdivided into groups by age including 5-7, 8-11 and 12-17 years old. These age groupings comprised of 24%, 38% and 38%, respectively, of the pediatric population evaluable for safety. The total number of subjects for each age ranged from 18 to 47. In the pivotal pediatric trial, 256 patients were evaluated for efficacy; 130 of whom received the Northstar system. Similarly, in Study (98NS-01-10, 48 patients were evaluated for efficacy; 23 of whom received the Northstar system.

There were sufficient numbers of subjects with a uniformly distributed population in terms of age to adequately label the Northstar system for use in the pediatric population aged 5 years and older.

8.4 Abuse Liability

Lidocaine and epinephrine have not been associated with psychological or physiological dependence. Neither component of the Northstar system has been identified or labeled as a controlled substance. The abuse liability of this product is therefore considered negligible.

8.5 120-Day Safety Update

The 120-day safety update indicated that there were no studies conducted or safety data collected since the NDA was submitted.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

APPENDIX A

The following items were still outstanding at the conclusion of the first review cycle.

Full evaluation of the following items received late in the review cycle:

1. Studies conducted under a _____ (summary reports submitted 7/18/03).
2. Revisions to ISS and ISE to correct for inconsistencies in subject numbers (submitted 7/18/03).
3. CRFs for subjects who discontinued studies due to adverse events (submitted 7/15/03)

Evaluation of the following items to be requested from the Sponsor:

1. An explanation for the high incidence of high skin impedance in study 98NS-01-10
2. An explanation for defining burns as a Draize erythema score of 4 (a serious adverse event by your definition), but then reporting no serious adverse events despite multiple reports of burns, including at least one 2nd degree burn, related to use of the patch.
3. An accounting for skin reactions not previously reported as AE's, e.g., in study 98NS-01-09, subject 915 had burns at all four application sites and subject 923 had skin removed by the patch adhesive at all four application sites per the DERMAL dataset, yet the adverse events dataset (ADVRE) contained none of these events.
4. A retabulation of the adverse events tables to include the points below as to allow for more appropriate product labeling.
 - Pain: Retabulate AE's to include all pain in one category with subcategories to include "pain NOS" and all unpleasant sensory AE's such as "application site burning" unless justification is provided otherwise. Resolve these events into those temporally associated with patch application, patch removal, procedure, post-procedure.
 - Burns: Justify creation of a separate "burns NOS" category and define entry to this category. Retabulate AE's to include all burns in one category with subcategories to include burns NOS.
 - All skin reactions: Present a tabulation of all skin reactions, with subcategories including rashes, erythema, burns, pallor/blanching, hematoma, sunburn, dermatitis, pruritis, etc.
 - Placebo groups: retabulate integrated AE tables to with separate incidence columns for "passive" placebos (i.e., no current) and for "active" placebos (with current).
 - Provide a comprehensive tabulation of adverse events for all studies of MIP II and III

APPENDIX B

The attached correspondence with the Sponsor were requests made during the review cycle for clarification and additional information.

-----Original Message-----

From: Compton, Kimberly
Sent: Thursday, July 10, 2003 6:16 PM
To: 'George Baskinger'
Subject: 7-10-03 requests

Hi George,

Below is a summary of our requests from our TC this afternoon.

1. Describe the safety features of the Northstar system to prevent current injury to the skin when a "high impedance" condition is encountered. Include the means used by the device to determine high impedance and what steps it takes to overcome the condition, i.e., ramping up of voltage. Include the maximum voltage the device can/will apply.
2. Provide an explanation for not reporting an adverse event in study 98NS 01-09 in which patient 98NS01-09-001-923 was noted as having "adhesive from the patch remove some skin" at all four application sites.
3. The comment in the "DERMAL" dataset indicates photos were taken of the injury described in #2 above. Send a copy of these photos for review.

Thanks,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthetic, Critical Care and
Addiction Drug Products (HFD-170)
301-827-7432

-----Original Message-----

From: Compton, Kimberly
Sent: Tuesday, June 24, 2003 12:47 PM
To: 'George Baskinger'
Subject: Clinical rqst (per TC) and Pharm/tox rqst (new) for NDA

Hi George,

As we discussed in our phone conversation this afternoon, I am forwarding you the request from Dr. Simone for additional information on pts not completing the studies.

In the meantime, I received an additional request for information from Dr. McGovern, our Pharm/tox Team Leader, who is also trying to finish his review and so I am forwarding that request as well.

We appreciate your turning these around quickly since the reviewers are trying to finish the drafts of their reviews, your fast response is very helpful.

Clinical:

1. What were the reasons that randomized subjects did not receive study treatment. Please include subject and study numbers.
2. Similarly, specify the reasons, ID numbers and study numbers for those who did not complete the studies.
3. Please send CRFs for all the above.

Pharm/tox:

1. Provide the formulation of the placebo and lidocaine patches used in the nonclinical studies GLP31736, GLP31737, GLP31738, and 32PD04.01; especially in regards to lidocaine and epinephrine content.
2. Provide a certificate of analysis for the lidocaine and epinephrine drug substance used in the above referenced nonclinical studies.
3. Specify the gender, age and body weights of the animals in the above referenced nonclinical studies.
4. Provide the individual animal data for study 32PD04.01.

Please let me know if any further clarification, etc. is needed.

Thanks,
Kim

-----Original Message-----

From: Compton, Kimberly
Sent: Thursday, June 12, 2003 5:57 PM
To: 'George Baskinger'
Subject:

Hi George,

Our medical officer has run into another data problem with the NDA.

Please look at the data for the study he has indicated and provide a response to us so he can complete his review as soon as possible:

Study BDTS99-25

Study report describes three treatments:

N* - active controller; active patch
AP - active controller; placebo patch
PP - inactive controller; active patch

The data tables report treatments as follow:

AA - active patch; active controller
AP - active controller; placebo patch
PA - placebo patch; active controller

What do the treatments AP and PA represent?

Submit an addendum clearly and consistently describing the items tested.

Please contact me with any questions or concerns.

Thanks,
Kim Compton

-----Original Message-----

From: Compton, Kimberly

Sent: Friday, June 27, 2003 1:18 PM

To: 'George Baskinger'

Subject:

Hi George,

As a follow-up to our phone call this morning, I am summarizing our request.

Dr. Simone noted reference in the NDA to early studies done with the product conducted in _____ and the Agency would like additional information on those studies.

While a full study report is not expected, the Agency always wants to see all safety related information on the products we review, including all patients that were exposed. Therefore please send us any safety information on the studies with the product, especially these studies that were conducted in _____, not under the US IND.

Thanks,
Kim

-----Original Message-----

From: Compton, Kimberly
Sent: Tuesday, July 22, 2003 3:00 PM
To: 'George Baskinger'
Subject: RE: 505(b)(2) Question

Hi George,

We need to know if you are referencing another NDA (drug) like Iontocaine (that was what we had in our notes from previous discussions) or just literature on lidocaine and epinephrine. (Either way you would still be a 505(b)(2) of course).

We need this as soon as you can get it.

Thank you,
Kim

-----Original Message-----

From: George Baskinger [mailto:gbaskinger@vyteris.com]
Sent: Tuesday, July 22, 2003 1:49 PM
To: ComptonK@cder.fda.gov
Subject: 505(b)(2) Question

Kimberly,

Can you please provide the question regarding the 505(b)(2) approach in writing by email?

Thank you,

George

-----Original Message-----

From: Compton, Kimberly

Sent: Thursday, June 19, 2003 5:55 PM

To: 'George Baskinger'

Subject: Another request for information

Hi George,

Dr. Simone asked me to have you clarify the differences (e.g., drug, current, adhesive, surface area, etc.) between the  and the MIP I, II, and III patches.

You can respond by email or in writing as you prefer.

Thanks!

Kim

301 827-7432

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

/s/

Arthur Simone
7/25/03 08:48:48 PM
MEDICAL OFFICER

Nancy Chang
7/25/03 08:53:57 PM
MEDICAL OFFICER